Immunohistochemical and Scanning Electron Microscopic Confirmation of the Lymphatic Lacunae in the Uterine Tube Mucosal Folds. What Are the Clinical Implications?

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Summary

Uterine tubes (UTs) are essential during physiological reproduction. The most intriguing part of its wall is the mucosa. Apart from the epithelial cells vital for its normal function, the connective tissue *lamina propria* contains wide spaces whose function, morphology and structure are yet to be elucidated. The present study used bioptic samples from 25 premenopausal (mean age 48.3 years, σ=3.56) and 25 postmenopausal women (mean age 57.8 years, σ=7.79). In both study groups, samples were obtained from two anatomically distinct parts of the UT – ampulla and infundibulum with fimbriae. The specimens were processed for scanning electron microscopy (SEM) and immunohistochemical detection of podoplanin (clone D2-40) and VEGFR-3 – two markers of lymphatic endothelial cells. The results showed that specimens from premenopausal and postmenopausal women contain wide lymphatic spaces, also known as lymphatic lacunae. The most probable function of the lacunae in the fimbriae is oocyte pick-up upon ovulation thanks to their ability to get engorged with lymph, thus serving as an erectile-like tissue. The ampullary lacunae are probably responsible for tubal fluid maintenance and recirculation. These results indicate that they are vital for normal reproduction because tubal fluid dynamics are as important as fluid composition. Further research on this topic is highly warranted because more detailed insights into UT function have a great potential to refine the methods of reproductive medicine, e.g. *in vitro* fertilization (IVF), which are still far from optimal regarding fertility outcomes.

Key words

Uterine tube • Lymphatic lacunae • Immunohistochemistry • D2-40 • Podoplanin • VEGFR-3 • SEM

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Introduction

Uterine tubes (UTs) are paired female internal reproductive organs essential during physiological reproduction [1]. For many years, the UT had been considered merely as a passive channel that only serves as a route for sex cells to reach each other and, in case of fertilization, as a pathway for the early embryo to reach the uterine cavity. This archaic concept is absolutely erroneous. Modern research on these unique organs has gradually revealed how dynamic UTs are [2]. The most intriguing part of the UT wall is its mucosa. It is lined with simple columnar epithelium composed of two, three or even four cell populations, according to different authors [3-5]. The two main populations are ciliated and non-ciliated secretory cells. The third one is a population of intercalated (peg cells), probably not an individual population, only a precursor or nonfunctioning subtype of secretory cells. The last one was formerly described as a population of basal cells, but our previous work revealed that they are, in fact, intraepithelial T lymphocytes [6]. The synchronized and dynamic cooperation of all these cells and other components of the tubal wall is necessary for such processes as oocyte pick-up, sperm and oocyte transport, sperm capacitation and hyperactivation, early embryonic development and many others [7-9]. Under the epithelial lining, there is a loose collagenous connective tissue called *lamina propria*, which is also very specific and different from loose collagenous connective tissue of other organs. It contains wide lymphatic spaces, also known as lymphatic lacunae, which were first described

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almost 120 years ago [10] but later forgotten and almost completely ignored in histological textbooks. We previously scrutinized these structures and immunohistochemically confirmed their positivity for podoplanin, evidenced by the antibody D2-40 [11]. Judging by their large size, topography and differences in the anatomical distribution in different parts of the UT, their functions probably differ from typical lymphatic capillaries found in other organs, which drain a tributary region into the regional lymph nodes, transporting immune cells and maintaining fluid balance [12]. It was hypothesized that they are responsible for the recirculation of tubal fluid. The second main probable role is that they transform the infundibular fimbriae into erectile tissue-like structures. When engorged with lymph, they can become thickened, which is helpful during oocyte pick-up upon ovulation [11]. The highly dynamic nature of the UTs is underlined by the fact that significant morphological and functional changes in the UTs occur in different life periods of women. It has been long known that not only the uterine mucosa undergoes hormonal changes, but the UTs do, too [13]. Thus, many insights can be acquired by studying the UTs from women of different ages. The thorough knowledge of the exact mechanisms occurring in the UTs is clinically significant, mainly due to the rising numbers of female factor infertility, which sometimes cannot be resolved even after using modern methods of reproductive medicine, like *in vitro* fertilization (IVF).

The main purpose of this immunohistochemical and electron microscopic study was to confirm the presence of the lymphatic lacunae in infundibular fimbriae and ampullae harvested from premenopausal and postmenopausal women and investigate the morphology and topography of these lymphatic spaces. To do so, freeze-fractured specimens were prepared for scanning electron microscopy (SEM). For immunohistochemical detection of lymphatic endothelial cells, podoplanin (D2-40) and VEGFR-3 were used. To the best of our knowledge, this is the first immunohistochemical and electron microscopic study examining lymphatic lacunae in the UTs from women in different life stages.

Material and Methods

Patients and uterine tube samples

The UT biopsies were harvested from 50 women (mean age 52.63 years, standard deviation (SD or σ) 7.53. 25 women were premenopausal (mean age 48.33 years, σ=3.56), and 25 were postmenopausal (mean age 57.8 years, σ=7.79). They all underwent laparotomic or laparoscopic salpingectomy, which was either solitary or accompanied by a hysterectomy. There was a broad spectrum of indications, including uterine fibroids, pelvic inflammatory disease, or uterine prolapse. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of the General hospital in Komárno, Slovakia. Informed consent was obtained from all patients.

Immunohistochemical staining

The bioptic samples were excised from two different anatomical parts of the UT, namely the ampulla and infundibulum with fimbriae. All samples were perioperatively fixed in 10 % formalin right after harvesting and were left in the fixative for 24 hours at room temperature. Then, all specimens were processed by the standard formalin-fixed, paraffin-embedded (FFPE) technique for hematoxylin and eosin staining and immunohistochemistry. For the latter, 5 µm thick tissue sections were boiled in citrate buffer for antigen retrieval. Afterwards, antibodies against podoplanin (clone D2-40) (Agilent DAKO) and VEGFR-3 (Bioss) (Table 1) were diluted and applied according to the datasheet provided by the manufacturers. Both are markers of lymphatic endothelial cells. The immune complexes of primary antibodies and respective antigens were visualized using EnVision FLEX Visualization System (Agilent Technologies, USA). The slides were counterstained with Mayer´s hematoxylin. All were examined using Leica DM3000LED light microscope, and the photomicrographs were captured using FLEXCAM C3 digital camera.

Scanning electron microscopy (SEM)

The bioptic samples for SEM were harvested and excised from the same ampullae and infundibular fimbriae as those processed for immunohistochemistry. The samples were fixed in buffered 3 % glutaraldehyde for 4 hours at room temperature. Then, the samples were rinsed in phosphate buffer three times and subsequently post-fixed in the solution of osmium tetroxide at 4 °C. After rinsing in demineralized water, the samples were dehydrated in a series of ethanols of ascending concentrations up to 100 % and dried at the critical point of liquid CO_2. Lastly, the samples were mounted on aluminum specimen stubs using carbon adhesive tapes, sputter-coated with a 15 nm gold/palladium layer and examined using ZEISS EVO LS 15.

Table 1. Characteristics of antibodies against VEGFR-3 and podoplanin (clone D2-40).

Antibody used	Manufacturer, code no.	Positivity
VEGFR-3	Bioss, BS-2202R	Endothelial cells of lymphatic vessels in normal tissues, and some neoplasms of lymphatic origin, e.g. Kaposi´s sarcoma [14]
D2-40	Agilent DAKO, M3619	Endothelial cells of lymphatic vessels in normal tissues, and some neoplasms of lymphatic origin, e.g. Kaposi´s sarcoma [15]

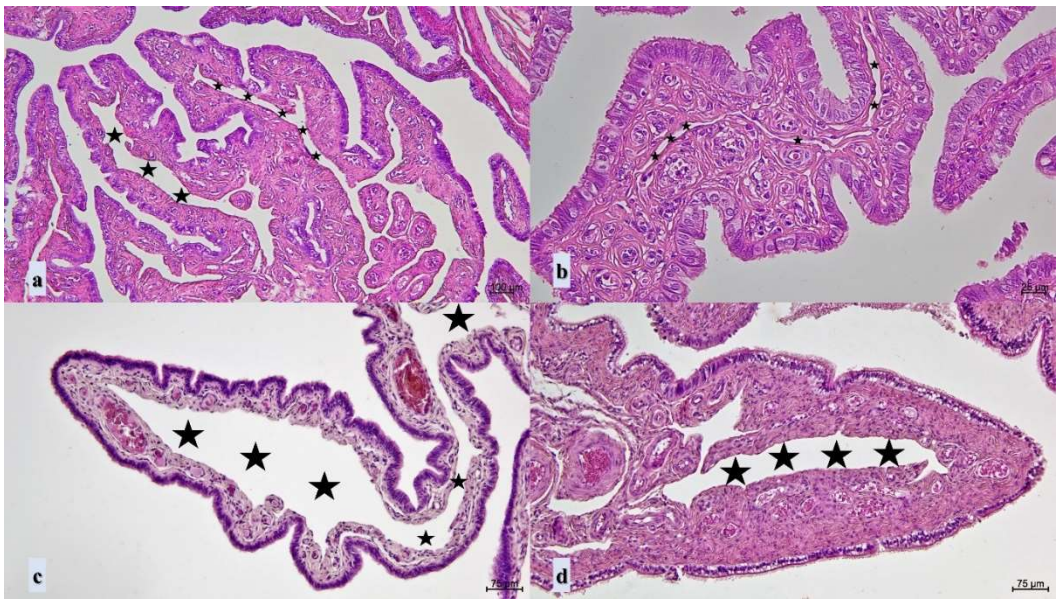

Fig. 1. HE-stained sections of ampullary portions (**a-b**) and infundibular fimbriae (**c-d**) of premenopausal (a,c) and postmenopausal (b,d) women. Wide spaces (black stars) are clearly visible within the *lamina propria* of the mucosa in both anatomical parts of the UT. Those in the infundibular fimbriae are significantly larger.

Results

Even the basic hematoxylin and eosin (HE) staining clearly showed that the *lamina propria* of the UT mucosal folds contains wide empty spaces of different course and width. The infundibular fimbriae had wider spaces, while the ampullary portion of the UT had narrower slits. At higher magnification, it was evident that these spaces were lined by flat cells in one layer, resembling endothelial cells. The specific feature in the ampullary portion was their presence in the center of most of the mucosal folds. The HE-stained ampullary portion and infundibular fimbriae in premenopausal and postmenopausal women are depicted in Figure 1.

The examination of SEM electron micrographs of freeze-fractured specimens demonstrated slit-like spaces within the *lamina propria* of the mucosal folds (Figs. 2, 3).

At a higher magnification, it is visible that the wide spaces are lined by a single layer of flat cells (Fig. 4).

The immunohistochemical staining confirmed that those spaces seen in HE sections and electron micrographs were lined by lymphatic endothelial cells detected using antibodies against podoplanin (clone D2-40) and VEGFR-3. Confirming the results of our previous study, D2-40 proved to be the most specific marker, clearly showing brown diaminobenzidine (DAB) staining exclusively reserved to endothelial cells of these wide lymphatic spaces in both the ampullae and infundibular fimbriae. VEGFR-3 also proved to be a reliable marker of lymphatic endothelial cells (Figs. 5, 6).

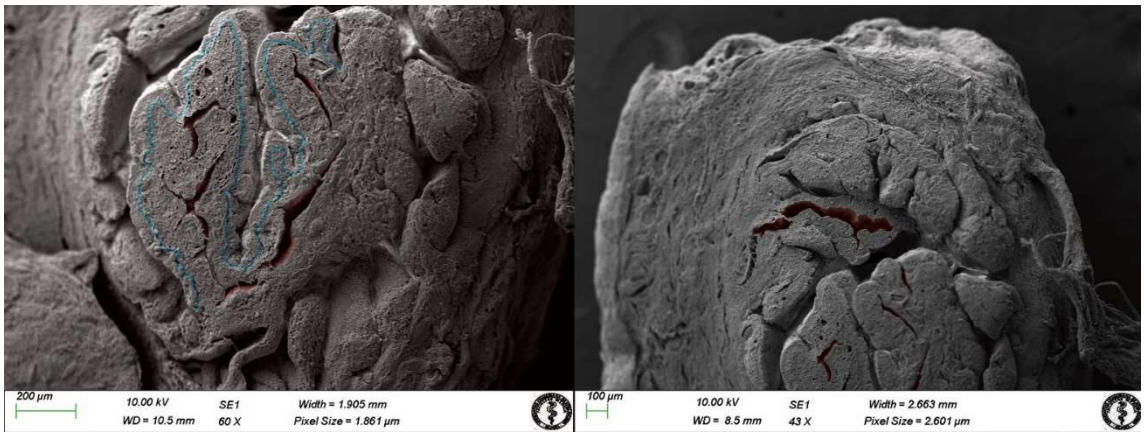

Fig. 2. SEM electron micrographs of ampullary portions of the UT of premenopausal (right) and postmenopausal (left) women. The blue outline on the left indicates the border between the epithelial lining and lamina propria of the mucosa. The images were post-processed (red color) to highlight the wide spaces located inside the *lamina propria.*

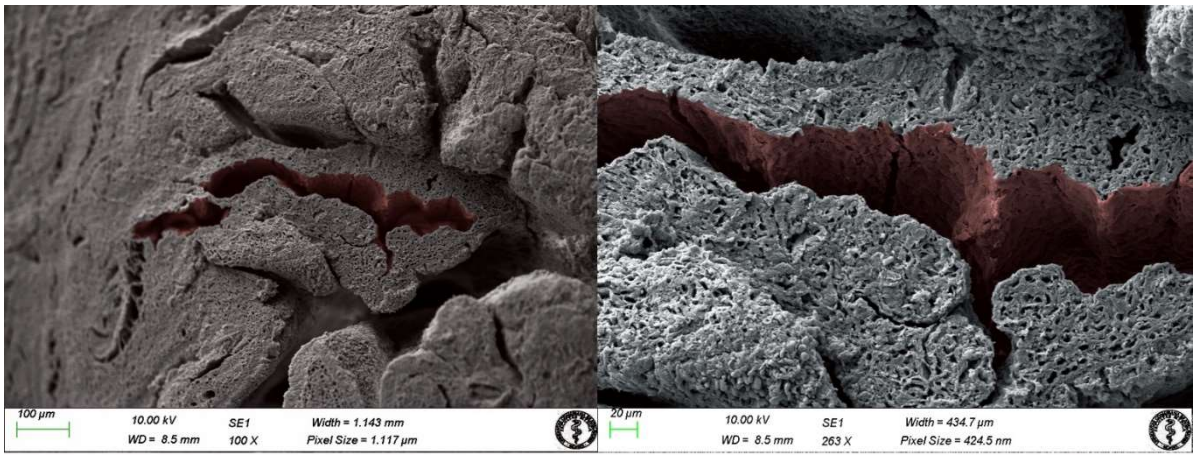

Fig. 3. SEM electron micrograph of an ampullary portion of the UT of a premenopausal woman. The images were post-processed (red color) to highlight the wide spaces located inside the *lamina propria*.

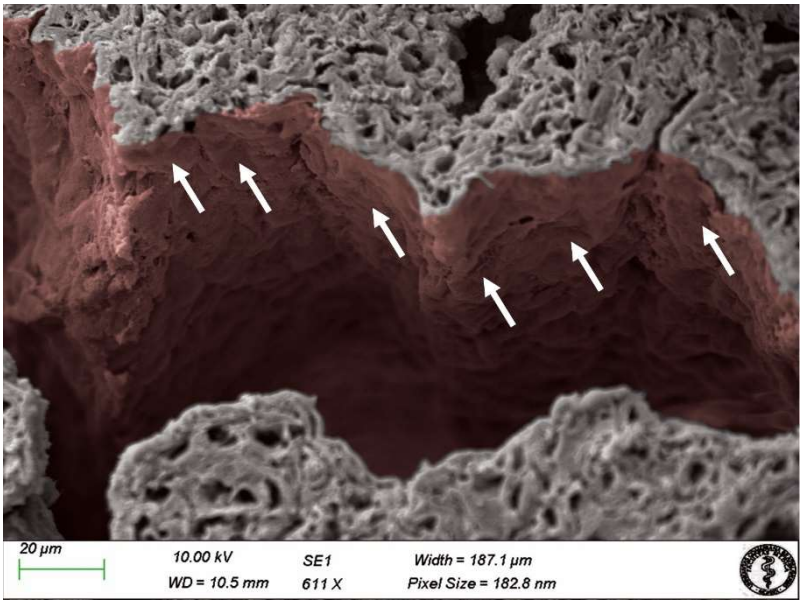

Fig. 4. SEM electron micrograph of an ampullary portion of the UT of a premenopausal woman. The higher magnification clearly shows that the wide spaces are lined by a single layer of flat cells, resembling endothelial cells. The images were post-processed (red color) to highlight the wide spaces located inside the *lamina propria*.

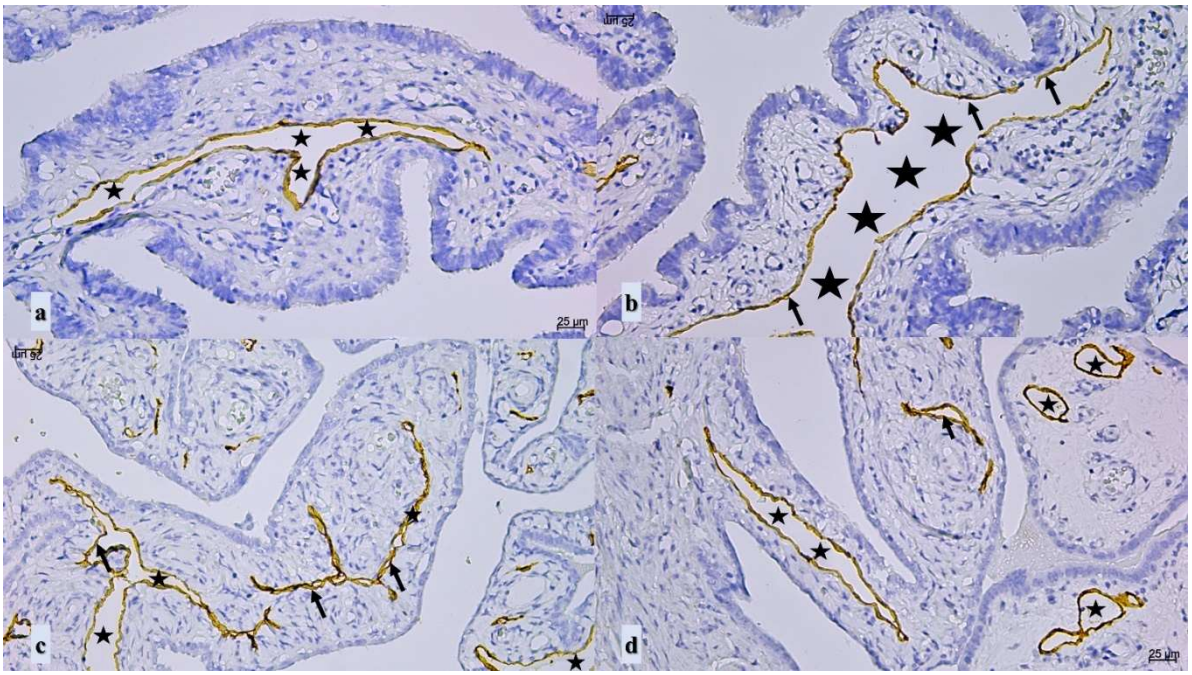

Fig. 5. Immunohistochemical visualization of the ampullary portions of the UT of premenopausal (**a-b**) and postmenopausal (**c-d**) women. The markers of lymphatic endothelial cells podoplanin (clone D2-40) (**a,c**) and VEGFR-3 (anti-VEGFR-3) (**b,d**) show that these wide spaces are in fact lymphatic lacunae.

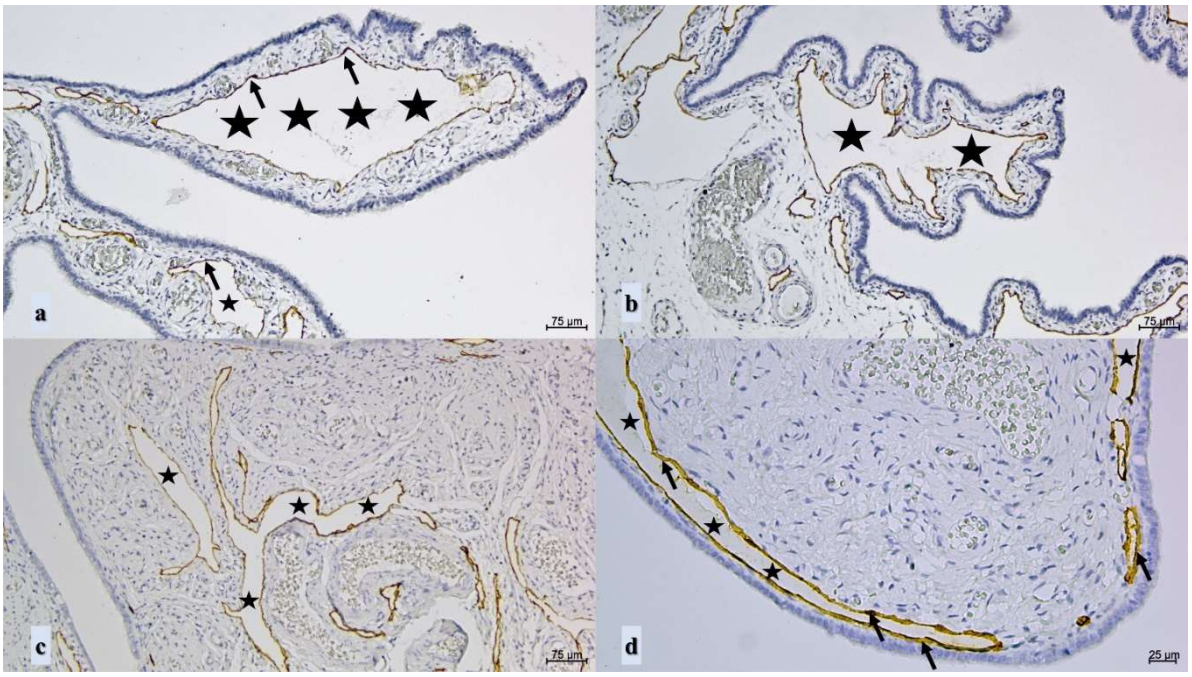

Fig. 6. Immunohistochemical visualization of the infundibular fimbriae of the UT of premenopausal (**a-b**) and postmenopausal (**c-d**) women. The markers of lymphatic endothelial cells podoplanin (clone D2-40) (**a,c**) and VEGFR-3 (anti-VEGFR-3) (**b,d**) show that these wide spaces are in fact lymphatic lacunae. The fimbriae of premenopausal women (**a-b**) contain significantly wider lymphatic lacunae compared to postmenopausal women.

Comparing premenopausal and postmenopausal women, the lymphatic lacunae were narrower in postmenopausal women. However, it could have been only a tissue-processing artefact. Nevertheless, if this finding is genuine, these differences can be easily corroborated by their probable functions discussed in the next section. Taken together, these results confirm that infundibular fimbriae and ampullae of the UTs contain wide lymphatic spaces of different morphology in premenopausal and postmenopausal women. As we previously suggested,

these structures should be named "lymphatic lacunae of tubal mucosal folds and fimbriae", with the Latin equivalent *"lacunae lymphaticae plicae mucosae et fimbriae"*. They should be included in the revised version of the *Terminologia Histologica* [11,16].

Discussion

The lymphatic lacunae of the UT mucosal folds were first described in the habilitation thesis of Paul Kroemer in 1904 [10]. From that year on, these structures have been rarely studied again. Most histological textbooks don´t mention them, and when they do, there is usually no information concerning their possible function or clinical significance [17-19]. The UT, in general, has become an overlooked organ mainly due to the successes of IVF techniques. This attitude is an unfortunate one mainly because any deeper insight into the UT function has the potential to improve the methodological aspects of the techniques of reproductive medicine. Moreover, UTs are also clinically relevant in gyneco-oncology. It is now widely accepted that high-grade serous ovarian carcinomas originate from the UT epithelial lining [20]. Discussing the clinical relevance of the lymphatic lacunae, several hypotheses exist regarding their function. Our previous research indicated that lymphatic lacunae in the infundibular fimbriae might have a role in oocyte capture during ovulation thanks to their ability to get enlarged due to lymph accumulated in the lacunae. The ampullary lacunae probably regulate tubal fluid recirculation [11]. This is highly relevant from the clinical perspective since the tubal fluid is the environment in which all the gestation-related processes occurring in the UT take place. Nowadays, it is generally accepted, despite the successes of IVF techniques, that naturally formed *in vivo* embryos are considerably different from and superior to those produced *in vitro*, which is reflected in poorer pregnancy outcomes of the latter and possible health complications later in life [21]. In 2018, Ferraz *et al.* [22] designed a study using a state-of-the-art oviduct-on-a-chip device which implemented the knowledge of the interdisciplinary field of microfluidics. The study design allowed for a more accurate emulation of the dynamic processes occurring in the UT during fertilization and early embryo development. One of the main "take-home messages" of the study was that the qualitative characteristics and contents of the tubal fluid are not the only important factor during fertilization and normal pre-implantation development. The regulation of dynamic flow and recirculation of the tubal fluid is possibly as important as the tubal fluid composition *per se*. The latest 2022 study used a similar approach. Wang *et al.* [23] implemented microfluidics technology by using a lab-on-a-chip device, which enabled the authors to mimic the dynamic *in vivo* environment inside the UT. One of the main findings was that the classic IVF techniques relying on static Petri-dish cultivation could not cope with various issues, e.g. the build-up of reactive oxygen species (ROS) that can originate from damaged blastomeres. The inability to effectively remove the ROS can harm DNA integrity and lead to deleterious epigenetic alterations. Therefore, a dynamic formation, absorption, or recirculation of the tubal fluid is vital for successful reproduction. These experiments demonstrate that the contribution of lymphatic lacunae to normal tubal fluid dynamics is clinically highly significant and should be addressed in future research. Other possible functions of the UT lymphatics were investigated in 1989 by Otsuki *et al.* [24]. They published an interesting immunoelectron microscopic study focused on the visualization of the UT lymphatic tissue and lymphatic vessels. They hypothesized that lymphatic "capillaries" might be the main migratory pathway of intraepithelial lymphocytes, mainly T lymphocytes. This notion is striking mainly in light of our previous immunohistochemical investigation of the immune makeup of the UT epithelial lining. We found that a population of "basal" cells, formerly thought of as a reserve of mitotically active cells responsible for epithelial regeneration, is a population of intraepithelial T lymphocytes, more specifically regulatory T cells. Their main clinically relevant function is probably immune supervision which ensures that the hemi-allogenic embryo won´t get rejected by the maternal immune system before it can reach the uterine cavity [6]. Discussing the possible functions of lymphatic lacunae in other organs, LeBlanc *et al.* [25] studied lymphatic lacunae in the uteruses of infertile mares susceptible to endometritis. The authors injected India ink into the uterine wall and cavity. They found that the normal clearance of matter from the uterine cavity by the lymphatics is impaired in the study group and might contribute to infertility. In 2008, Red-Horse [26] reviewed the dynamics of lymphangiogenesis in the uterine wall during pregnancy. Strikingly, the non-pregnant endometrium lacks well-developed lymphatic circulation. However, decidual changes in the endometrium stimulated by the trophoblast of the implanting embryo include pronounced lymphangiogenesis. The exact roles of these changes are not entirely clear. The most probable functions are fluid

homeostasis and immune regulation. Lymphatic lacunae were also studied in organs outside the female reproductive system, such as the eye. In a recent 2020 study, Nicolescu *et al.* [27] found that the human eye conjunctiva also contains such lymphatic spaces. Unfortunately, the authors did not mention any possible functions. Interestingly, the authors also discussed the population of interstitial cells of telocytes which are located in the interstitium of most organs of the human body. These cells possess long cytoplasmic projections called telopodes, which can sometimes be confused with lymphatic capillaries when caught in a tangential section. Based on this caution, many research teams focusing on telocyte study have tried distinguishing telocytes from lymphatics by implementing specific lymphatic immunohistochemical markers, e.g. those used in the present study [28]. Even though the main goal has been to confirm the genuine presence of telocytes in the studied locations, we expect that such future research endeavors will indirectly elucidate the lymphatic circulation in various organs and contribute to a better understanding of the different functions it might have. In 1996, Li *et al.* [29] performed an electron microscopic investigation of the subperitoneal lymphatic lacunae. The main finding of their study was that lymphatic lacunae are in close contact with mesothelial cells lining the peritoneal cavity and are responsible for the absorption of various substances and materials from within the peritoneal cavity. All in all, it seems that the most significant role of lymphatic lacunae is the fluid homeostasis and dynamics not only within the interstitial space by also between the organ cavity and its wall. This is especially significant for the normal function of the UTs during reproduction, as evidenced by the above-discussed studies.

Conclusions

The role of lymphatic circulation in the UTs has been a topic that few research teams have been paying attention to. The main reason is that UTs, in general, are not at the forefront of research interest, mainly due to their presumed needlessness in light of the modern achievements of reproductive medicine. This attitude should be completely abolished for several reasons:

- the exact functioning of the UT environment concerning early gestation-related processes is still far from thoroughly understood,
- the IVF is unable to precisely emulate the tubal fluid composition and dynamics, leading to pregnancy outcomes that are far from optimal,
- lymphatic lacunae of the tubal mucosal folds probably have an important function in tubal fluid dynamics which is as important as its composition, but their exact role in this process is underresearched,
- any deeper insights into the tubal fluid dynamics can significantly improve the success rate of IVF techniques,
- the proper tubal fluid environment might influence such processes as epigenetic reprogramming and gene expression patterns which may impact not only the pregnancy outcomes but possibly also the health status of an individual postnatally or even later in life.

All these reasons provide clear evidence that lymphatic lacunae of the UTs, or the UTs as a whole for that matter, should not be overlooked and need to be studied thoroughly within the basic research due to many potentially beneficial translations into clinical settings.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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