REVIEW

From a Passive Conduit to Highly Dynamic Organ - What are the Roles of Uterine Tube Epithelium in Reproduction?

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Summary

It is well known that the mammalian uterine tube (UT) plays a crucial role in female fertility, where the most important events leading to successful fertilization and pre-implantation embryo development occur. The known functions of these small intra-abdominal organs are: an uptake and transport of oocytes; storage, transportation, and capacitation of spermatozoa, and finally fertilization and transport of the fertilized ovum and early embryo through the isthmus towards the uterotubal junction. The success of all these events depends on the interaction between the uterine tube epithelium (UTE) and gametes/embryo. Besides that, contemporary research revealed that the tubal epithelium provides essential nutritional support and the most suitable environment for early embryo development. Moreover, recent discoveries in molecular biology help understand the role of the epithelium at the cellular and molecular levels, highlighting the factors involved in regulating the UT signaling, that affects different steps in the fertilization process. According to the latest research, the extracellular vesicles, as a major component of tubal secretion, mediate the interaction between gametes/embryo and epithelium. This review aims to provide up-to-date knowledge on various aspects concerning tubal epithelium activity and its cross-talk with spermatozoa, oocytes and preimplantation embryo and how these interactions affect fertilization and early embryo development.

Keywords

Embryo • Epithelium • Fertilization • Immune system • spermatozoa • Tubal fluid • Uterine tube •

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Introduction

Uterine tubes (UTs) are important organs of the female internal reproductive system, responsible for cardinal processes needed for successful reproduction including the uptake and transport of oocyte, storage, transportation, and capacitation of spermatozoa, fertilization and transport of fertilized ovum and early embryo through the isthmus towards the uterotubal junction [1]. For a long time, uterine tubes (UTs) had been inevitably necessary for a successful conception. Without them, there was no hope females to bear a child, because the medicine of past times failed presenting ways to bypass this important organ. Nowadays, the situation has changed drastically owing to the modern methods of reproductive medicine [2]. From one extreme of absolute importance, some experts came to the other extreme of considering the UT superfluous, because most of the processes occurring in the UTs during fertilization and early embryo development can be successfully reproduced *in vitro*. In spite of that, UTs are still far superior in promoting and maintaining the early pregnancy, compared to anything that we have managed to mimic in laboratory conditions [3]. Moreover, a number of processes and interactions between UTs and its contents are significantly underresearched, so there is still a great potential to

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discover something new that would deepen our understanding of the early stages of gestation, bringing clinically significant knowledge into the fields of gynecology and reproductive medicine.

The specific part of the UT wall that is paramount in proper orchestration of its functional roles is the uterine tube epithelium (UTE). This review article aims to provide up-to-date knowledge concerning the UTE and its cross-talk with spermatozoa, oocyte and preimplantation embryo.

Terminological peculiarities

According to the official histological nomenclature *Terminologia Histologica* [4], UTs should be the proper designation for these important female internal reproductive organs. Nevertheless, especially in the English literature, there are several other names that are often preferred like oviducts, and one is especially common – Fallopian tubes. This is rooted in a very colorful history of the discovery and research of this peculiar organ. In the 16th century in the Italian city of Modena, Gabriele Fallopio (1523-1562), an exceptionally talented anatomist was born. He rose to recognition and fame by becoming a professor of anatomy, surgery and botany at the University of Padua, Italy. His immense skills in anatomical dissection brought many important discoveries. One of the most interesting was his observation and description of "semen-conveying ducts" that reminded him of a brass trumpet (tuba in Italian). This organ later became known as the Fallopian tube – a designation used to this very day [5,6]. In spite of that, the authors of this paper will use the official term – UTs, solely for the sake of sticking to the official nomenclature, without any intention to disregard the great contributions of the renowned anatomist and physician.

The latest knowledge on the structure and function of uterine tube epithelium

UTE is histologically defined as simple columnar epithelium. Histology textbooks often distinguish two, three or even four different types of epithelial cells. According to the latest edition of *Terminologia Histologica* [4], the four types of epithelial cells are ciliated cells *(epitheliocytus ciliatus)*, secretory cells *(exocrinocytus tubarius)*, peg cells *(epitheliocytus tubarius angustus)*, and finally basal cells *(epitheliocytus tubarius basalis)*. The following paragraphs will briefly mention their morphological and functional aspects, as well as the most recent knowledge on their nature and complex interrelations.

Morphological and functional aspects of ciliated cells – ciliogenesis, deciliation, and ciliary beating

Ciliated cells are named as such because they possess one defining characteristic - motile projections at their apical pole. Thanks to these, ciliated cells can successfully perform their transport function. Comparing them to other ciliated epithelia (e.g. in trachea) they have one additional unique feature. The ciliary beating direction has to be distributed in a specific pattern to allow bidirectional movement, both towards and away from the uterus. This peculiar feature facilitates the opposite flow of spermatozoa vs. oocytes and preimplantation embryos [7]. It has been long known that ciliated cells are unevenly distributed in different anatomical parts of the UT and undergo morphological and functional changes according to the phase of menstrual cycle, gestation, as well as the reproductive age. Ciliated cells are most abundant in the fimbriae (around 50 %), followed by the ampulla, while in the isthmus region, only 30 % of cells account for the ciliated type [8]. Cilia turnover occurs by two opposing processes – ciliogenesis and deciliation. In 1992, Hagiwara *et al.* [9] investigated how ciliogenesis in human UTs correlate with the normal menstrual cycle. The replication of basal bodies and protrusion of ciliary shafts was observed primarily during the proliferative phase. A surprising finding of the study was that the cells undergoing ciliogenesis had vesicles resembling secretory granules inside the cytoplasm, suggesting that ciliated cells and secretory cells might in fact be counterparts transdifferentiating on demand [9]. A more recent study unveiled the molecular mechanisms involved in the process. Zhu *et al.* [10] showed that multi-ciliated cells differentiate under the guidance of epidermal growth factor (EGF) and estrogen, acting through the Notch signaling pathway. While the former suppressed ciliogenesis, the latter induced it. Challenging the predominant notion that ciliated and secretory cells differentiate form two separate progenitors, Gosh *et al.* [11] performed *in-vivo* genetic cell lineage tracing that substantiated the hypothesis that secretory cells indeed differentiate into ciliated cells and also demonstrated their self-renewal capacity. Although the study was performed using mouse UTs, a recent 2021 study proved that it also applies to human subjects. Dinh *et al.* [12] investigated 53,000 individual cells using single-cell transcriptomic

profiling that revealed ten epithelial subpopulations expressing different markers based on their actual differentiation state, with two subpopulations of transitioning cells between clusters of secretory and ciliated cells.

Another important functional aspect of ciliated cells is ciliary beating frequency (CBF). Up to this day, numerous *in-vitro* and *in-vivo* studies have been published, enlightening the more detailed view of this essential transportation process which is regulated by various factors, such as neuronal factors, locally released signals, ovarian steroids, or embryo-secreted factors (the latter will be discussed in a separate section). For instance, cilia stimulation can be attributed to angiotensin II-activated angiotensin II receptors [13], or autocrine platelet activating factor (PAF)-stimulated secretion of prostaglandins (PGE2, PGF2α) by the UTE [14]. Another important molecule that stimulates ciliary beating is adrenomedullin, whose expression is hormone-dependent and is stimulated by spermatozoa [15]. Regarding the hormonal regulation, it is known that the concentration of ovarian steroids in the UT is much higher due to the countercurrent vasculature system between the ovary and UT, suggesting that estrogen and progesterone levels can promptly affect the CBF [16]. Nakahari *et al.* [17] confirmed this notion by observing the UTE using high-speed videomicroscopy. The administration of medroxy progesterone decreased the CBF, while β-estradiol benzoate increased it by a small amount.

Morphological and functional aspects of secretory cells – production of tubal fluid and role in the pathogenesis of high grade serous ovarian carcinoma

As their name suggests, secretory cells are responsible for exocrine secretion of various substances that are a part of the tubal fluid, where all the gestation-related processes occurring in the UT take place. Since they do not possess motile cilia at their apical surface it is an easy task to distinguish them from ciliated cells even at the level of light microscopy. Using scanning electron microscopy, this task is facilitated [18]. Nevertheless, as mentioned above, novel line of research indicates that that these two cell populations are in fact distinctive differentiation variants of one progenitor cell, transitioning back and forth based on actual functional needs [12]. Over the last years, multiple studies confirmed one clinically relevant aspect of secretory cells which is that they can become the cells of origin of high grade serous "ovarian" carcinoma (HGSOC) [19,20].

Peg cells – a unique cell population or merely a functional variation of secretory cells?

Peg cells have been historically described as the third type of cell of the UTE (UTECs) [21]. Another synonym used interchangeably in literature is intercalated or intercalary cell, because these slender cells with a tiny amount of cytoplasm are typically wedged in between ciliated and secretory cells [22]. Later research challenged the individuality of peg cells, considering them only a precursor or nonfunctioning variant of secretory cells [23]. In contrast, Paik *et al.* [22] isolated these cells and hypothesized that peg cells are regenerative cells of the UTE with stem-like properties and can also have a role in carcinogenesis.

Basal cells – stem cells or intraepithelial T-cells?

Based on the discrepancies regarding the nature of basal cells, Varga *et al.* [24] performed an immunohistochemical study which brought a surprising finding. Immunostaining for immune system markers revealed that basal cells are not undifferentiated stem cells, as they are usually described in literature, instead they were identified as intraepithelial regulatory (suppressor) T-cells, perhaps playing an important role in triggering the immune tolerance towards the hemiallogeneic early embryo. These new insights will probably be applied to the upcoming revised edition of *Terminologia Histologica*, replacing the original term - basal cells *(epitheliocytus tubarius basalis)* with intraepithelial T-cells *(lymphocytus T intraepithelialis tubarius)* [24].

Uterine tube epithelium and spermatozoa

In the early 1950s, independent of each other, Austin [25] and Chang [26] published interesting observations revealing that for spermatozoa to successfully fertilize the oocyte, they must undergo some yet unknown processes that occur after they spend some time in the female reproductive organs. Later in 1952, this set of physiological changes was termed "capacitation" by the former of the two researchers [27]. This initial knowledge and later research eventually led to the development of fertilization techniques that were able to reproduce the environment and conditions necessary for capacitation *in vitro* [28]. The two main changes that occur during capacitation are hyperactivation, and changes enabling the acrosome reaction. Hyperactivation is characterized as a modification of sperm movement patterns, and the acrosome reaction-enabling changes

include various molecular-level adjustments mostly concerning the plasma membrane such as an increase in fluidity, hyperpolarization, or the loss of cholesterol [29]. Over the 70 years that have passed from its initial description, a vast bulk of knowledge has been obtained from description of interactions between spermatozoa and different parts of the female internal reproductive organs, to the molecular mechanisms behind these peculiar modifications. Nevertheless, many mechanisms underlying capacitation are still only partially understood. One of the most challenging issue is to elucidate which exact parts of the female reproductive organs and to what extent play a role in different capacitation steps. In 2000, Kervancioglu *et al.* [30] investigated the role of UTE on capacitation. The authors created a cell culture to study the influence of physical contact between spermatozoa collected from voluntary donors and UTECs. After 24 hours of cocultivation, spermatozoa exhibited pronounced changes in different motility characteristics including curvilinear velocity and amplitude of lateral head displacement. When the experimenters placed microporous membrane into the culture preventing cell-to-cell contact, all these effects were hindered. Thus, the results indicated that direct contact between spermatozoa and UTECs are vital for capacitation [30]. Recently, Massa *et al.* [31] identified a specific protein S100 A9. Upon performing a wide array of methodological approaches, the authors concluded that S100 A9 is expressed in the UTE and is also present in tubal fluid. It was demonstrated that S100 A9 binds to oocytes and spermatozoa alike, while in the latter it was shown to activate different molecular mechanisms involved in capacitation [31]. An emerging modern line of research is that focused on different types of extracellular vesicles (EVs). Franchi *et al.* [32] studied EVs obtained from bovine tubal fluid, namely from the isthmus and ampulla. They found out that EVs participate in various processes related to sperm capacitation. EVs interacted with spermatozoa, maintained their viability, stimulated the induced acrosome reaction, and regulated capacitation-associated signalling pathways like protein tyrosine phosphorylation and intracellular calcium increase [32]. Although this study did not specify the origin of these EVs, recent papers suggest that they originate from the UTECs [33].

Another important aspect of successful fertilization is the immunological adaptation with the ultimate goal to prepare a suitable immune-friendly environment for establishment and maintenance of early pregnancy. Immunological interactions occur in all the participating components involved in the fertilization and initial embryo development, including the interaction between UTECs and spermatozoa. Liu *et al.* showed that bovine tubal fluid contains neutrophilic granulocytes that are unresponsive towards the spermatozoa in terms of their phagocytosis. The authors showed that a major acute-phase protein alpha 1-acid glycoprotein (AGP) plays a crucial role in this regard. AGP was found to be produced by UTECs, preventing the sperm phagocytosis. AGP also induced the production of prostaglandin E_2 in the UTECs that provided an additional supression of phagocytosis by neutrophilic granulocytes.The bottom line was that UTEC-derived secretory products are cardinal in the immunomodulation protecting the spermatozoa from being attacked by the immune system [34]. The same role of UTEC-derived prostaglandin E_2 on downregulation of bovine sperm phagocytosis was confirmed by Marey *et al.* [35]. Zandieh *et al.* [36] used human immortalized tubal epithelial cell line OE-E6/E7 as a *in-vitro* model to study the immunological cross-talk between UTECs and spermatozoa. The main finding was that toll-like receptors (TLR) 3 and 5 in the epithelial cells are activated by spermatozoa. TLRs are pivotal components of the innate immune system and play important roles in ovulation, capacitation and fertilization. In the present study, the upregulation of TLR 3 and 5 as well as the production of different cytokines provided first evidence about the mechanisms of immunological interaction between spermatozoa and UTECs necessary for providing a hospitable environment for a successful fertilization and early embryo development [36]. Mousavi *et al.* [37] also used the OE-E6/E7 cell line to study the UTEC expression of different cytokines, chemokines and growth factors in the presence of spermatozoa. The measurements affirmed that spermatozoa have profound influnce on expression profiles of different inflammatory markers of UTECs that enable the local microenvrionment to gravitate towards the establisment of anti-inflammatory conditions favourable for allogenic spermatozooa to survive and fulfill their irreplaceble role in fertilization [37].

Uterine tube epithelium and oocyte

Upon ovulation, the oocyte is picked up by the fimbriae of the infundibulum. This happens by various mechanisms, most interestingly, the process is facilitated by thickening of the fimbriae that become engorged with lymph thanks to recently rediscovered, special lymphatic spaces termed lymphatic lacunae [38]. Very important to

note is that oocyte is not the only cell released from the ovary. Oocyte is directly surrounded by granulosa cells called *corona radiata* that from a part of the "egg-bearing little cloud" - *cumulus oophorus* of the mature Graafian follicle. Upon ovulation, oocyte is released along with granulosa cells of *corona radiata*, forming a complex which is commonly termed, cumulus-oocyte-complex (COC). When discussing the interaction between UTECs and oocyte, it is necessary to take into consideration the complex as a whole. Cumulus (corona) cells (CCs) and COC extracellular matrix are essential for the picking up and initial adhesion of oocyte to the infundibular cilia, whereas only slight changes in the level of COC could cause adhesion difficulties [39,40]. Based on electron microscopic analyses, the adhesion takes place solely between the tips of cilia and the filaments of the extracellular matrix of COC and is highly specific because COC does not adhere to other types of ciliated cells [41,42]. Another recently described interaction between human oocyte and UTs is via oviduct-specific glycoprotein (OVGP1)/ oviductin, which has been identified in tubal fluid and is secreted by secretory cells. OVGP1 is not present in ovarian follicles; however, it binds to the zona pellucida of post-ovulatory oocytes [43]. Several animal *in-vitro* studies have demonstrated the positive effect of OVGP1 on fertilization. For example, polyspermy in pigs was significantly reduced after pre-treatment of the oocyte with low concertation of oviductin. It is believed that mentioned polyspermy reduction by OVGP1 is caused by functional changes in *zona pellucida*, thus making it more resistant to enzymatic digestion and sperm penetration [44]. Likewise, results published by Kouba *et al.* [45] showed high penetration rate and decreased polyspermy in porcine oocytes treated with medium supplemented with OVGP1. Based on knowledge from animal experiments, Zhao *et al.* [46] synthesized for the first time recombinant human oviductin (rHuOVGP1), which was very similar to the native human OVGP1. It was found that there are also other tubal proteins with comparable positive effect on polyspermy elimination, including osteopontin, or deleted in malignant brain tumors 1 [47,48]. These results could potentially help to improve assisted reproduction techniques, further increasing fertilization success. More recently, it was described that EVs and microvesicles (MVs) play an important part not only in embryo-UT interaction but also modulate interactions between oocyte and UT [49]. Lange-Consiglio *et al.* [50] studied the effect of MVs secreted by UTECs in canine oocyte maturation *in vitro* and found out that three specific microRNAs (miR-30b, miR-375 and miR-503) which are part of MVs cargo material, play critical roles in follicular growth and oocyte maturation [50]. More recently, Lee *et al.* [51] demonstrated the effect of canine tubal EVs on oocyte development via EGFR/MAPK pathway *in vitro*. The authors observed enhanced COC proliferation and oocyte maturation rate. Taken together, according to this knowledge, the supplementation of cultivation media with MVs and EVs can have a significant impact on the success rate of *in vitro* fertilization (IVF) techniques [51].

Uterine tube epithelium and early embryo

The idea that UTs are merely a passive conduits has been progressively overthrown by still growing body of research on these fascinating organs. In human studies and animal models alike, it has been repeatedly demonstrated that after coculturing preimplantation embryos with UTECs, many important aspects of early gestation are positively influenced including the quality of inner cell mass, or the rate of successful implantation. Apparently, these effects are bidirectional – not only the UTECs influence the embryo, it also reciprocally influences the UTECs [52].

Although hard to estimate, as many as 60 % of all pregnancies might end prematurely. The tricky part about it is the fact that a significant portion of this number accounts for pre-implantation pregnancy losses that go unrecognized because they happen sooner than a women is able to suspect anything out of the ordinary, as the "normal" mestrual bleeding of the next cycle obscures the fact that the conception did in fact occur [53]. It has been long known that following implantation, the early embryo actively communicates with the maternal tissues in a highly complex and orchestrated manner by different mechanisms including EVs, endocrine and paracrine signalling [54]. The fact is that this communication begins way sooner than the embryo begins to implant into the secretory phase endometrium. Without any doubt, as suggested by multiple lines of research, the interaction between embryo and maternal tissues starts right after the fertilization and involves mainly the UTECs. Therefore, the understading of this cross-talk and its possible disorders is of utmost importance for understanding the normal reproduction as well as associated pathologies [55]. For proper insights into all the gestation-related processes occuring in the UT, it is inevitable to understand the secretion, composition, dynamics and function of the

tubal fluid, because it is the stage where all these processes take place. Even though some of its components originate from the follicular fluid, most of it formed from blood plasma or interstitial fluid that is transported through the epithelial lining, while some constituents are secreted by the UTECs themselves [56]. In any case, it contains a complex spectrum of molecules including hormones and nutritive sustances that are neccessitated at a given time. Smits *et al.* [57] authored a comparative study, investigating the proteome of equine tubal fluid. After comparing contralateral (control) and ipsilateral (embryo-containing) UTs, the authors found that the presence of embryo induced differentiated up- and downregulation of expression of various genes, indicating that the embryo itself affects the composition of the tubal fluid [57]. Kölle *et al.* [58] used scanning electron microscopic investigation of bovine UTs in order to quantitatively assess the ratio of ciliated to secretory cells in different parts of the UT with respect to the transiting embryo. Based on the proportion of cilliated vs. secretory cells according to its actual whereabouts, the results indicated that the embryo was able to induce the differentiation of secrectory cells in a given anatomical part of the UT. The embryo also affected the vascularization pattern of *artreria tubae uterinae* [58]. It is generally accepted that the transit of embryo inside the UT towards the uterotubal junction is carried out by three mechanisms: 1) cilliary beating, 2) flow of tubal fluid and 3) smooth muscle contractions. Only recent research endeavours highlighted that the embryo itself can regulte its own transit by affecting these means of transport [59]. As already mentioned, highly intricate immune system adjustments at different levels are vital during all gestation-related processes occuring in the UT. Immune system changes also result from a complex interplay between UTECs and embryo. Talkuder *et al.* [60] investigated *in vitro* the changes in bovine UTECs when cocultured with IVF-obtained embryos. The principal finding was that the UTECs induced the expression of interferon-tau in embryos after 4 days of cultivation. Subsequently, this immunosupressive cytokine promoted anti-inflammatory signalling inside the UT, contributing to the immune changes necessary for the hemiallogenic embryo to dodge the recognition as non-self by the maternal immune system [60].

All the interactions between UTECs, spermatozoa, oocytes and early embryos are depicted in Figure 1.

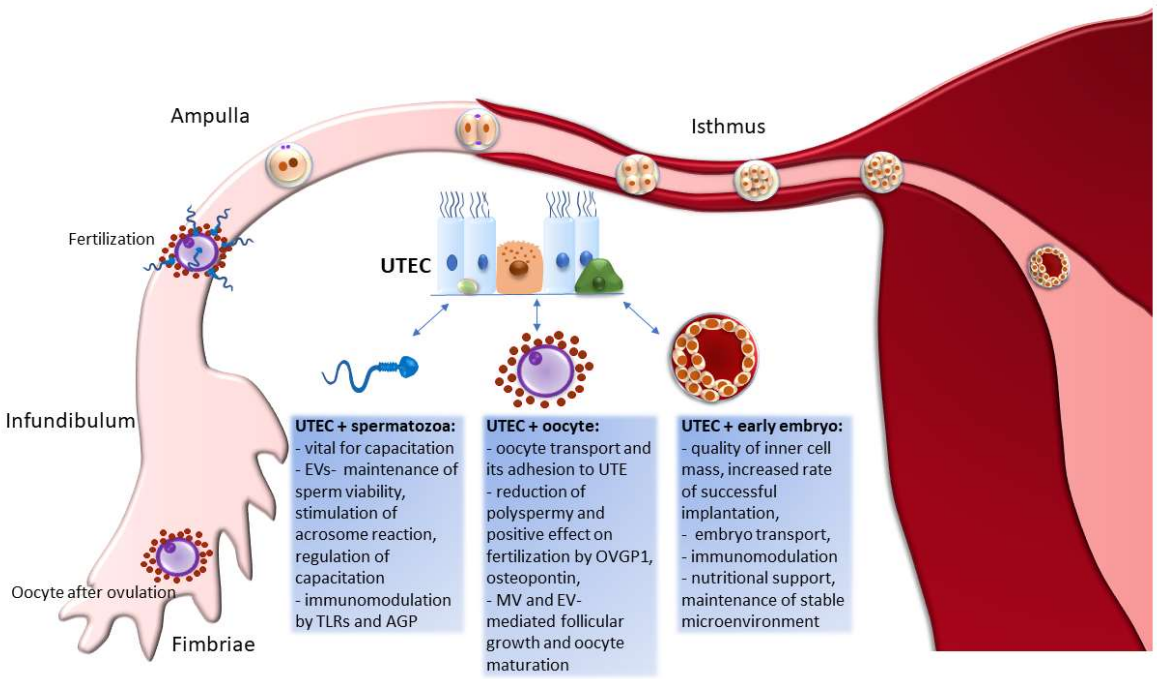

Fig. 1. Cross-talk between uterine tube epithelium and spermatozoa, oocyte and early embryo during fertilization and preimplantation development.

Conclusions and future perspectives

The latest research has clearly shown that the obsolete notion of UTs as passive conduits could not be further from the truth. The active cross-talk between spermatozoa, oocytes, preimplantation embryos and UTECs occur before, at, as well as after fertilization, but also during the transit of the cleaving zygote towards the uterus. Therefore, the understanding of all these processes and its translation into clinical practice has massive impact on the further development of the whole field of reproductive medicine. Ongoing research endeavors in this regard are highly warranted because any additional insights will provide an opportunity for the implementation of new IVF techniques, refining the already extremely successful medical field. This is absolutely up-to-date since the rates of infertility are on the rise around the globe, making IVF one of the most scrutinized and sought-after medical procedures the modern evidence-based medicine has at its disposal.

Conflict of Interest

There is no conflict of interest.

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