Tubal transport of gametes and embryos: a review of physiology and pathophysiology

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Abstract With the advent of assisted reproductive technology in the past three decades, the clinical importance of fallopian tubes has been relatively overlooked. However, successful spontaneous conception requires normal function of the tube to provide not only a conduit for the gametes to convene and embryo to reach the uterine cavity, but also a physiologically optimized environment for fertilization and early embryonic development. In this review, after a brief description of normal human tubal anatomy and histology, we will discuss tubal transport and its principal effectors, including ciliary motion, muscular contractility and tubal fluid. Furthermore, we will discuss the ciliary ultrastructure and regulation of ciliary beat frequency by ovarian steroids, follicular fluid, angiotensin system, autonomic nervous system and other factors such as adrenomedullin and prostaglandins. In the last section, we describe the adverse impact of various pathological conditions, such as endometriosis, infection and smoking on tubal function and ciliary motility.

Capsule Tubal transport of gametes and embryo requires coordinated actions of ciliary movement, tubal peristalsis and tubal fluid. Ciliary movement is controlled by many different signals and can be adversely affected by a variety of conditions such as endometriosis, infection and smoking.

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Introduction

Over the recent years, the role of the fallopian tube has been underestimated; with the introduction of assisted reproductive techniques, the fallopian tube is being represented as an abandoned anatomical structure that is bypassed by in vitro fertilization.

In order to successfully achieve a spontaneous pregnancy, a complex system of tubal transport must be operational to allow a timely interaction between gametes and subsequently provide a conduit for the developing conceptus to reach the uterus. Three different components, ciliary motion, muscular contractility and tubal fluid, all contribute to varying degrees to effective tubal transport.

The purpose of this review is to elaborate on the most recently identified regulatory mechanisms of tubal transport as well as factors that can adversely affect this process and thereby compromise chances of successful pregnancy. The physiological regulation of ciliary motion in the fallopian tube and the pathological states that can potentially cause altered or impaired ciliary activity will be discussed in detail.

Normal anatomy and histology of the fallopian tube

Embryology and development of the fallopian tube

Between weeks five and six after oocyte fertilization has taken place, a longitudinal groove, called 'Müllerian Groove', forms from the coelomic epithelium on the lateral sides of the mesonephric duct. Fusion of the edges of Müllerian Groove forms the Müllerian or paramesonephric duct. The fallopian

tubes originate from the most cephalad portion of the paramesonephric ducts. Their cranial ends are open and connect with what eventually will form the coelomic (peritoneal) cavity. The caudal end communicates with the uterine cavity [1].

Gross anatomy of the fallopian tube

The fallopian tubes are tubular seromuscular organs that are located in the upper margins of the broad ligament between the round and the uteroovarian ligaments. The average tube measures 9–11 cm in length. At its opening into the peritoneal cavity there are approximately 25 finger-like projections known as the fimbriae [2].

Fallopian tube consists of four segments; from lateral to medial, these segments include 1) the infundibulum, 2) the ampulla, which comprises the major portion and more than half of the length of the tube, 3) the isthmus and 4) the interstitium (Fig. 1). The interstitium, which is also known as the intramural part continues from the isthmus through the uterine wall and transverses the uterine muscle [2, 4].

Histology of the fallopian tube

The fallopian tube is composed of three layers: an inner mucosal surface, a wall of smooth muscle and an outer serosal layer. The mucosal surface of the fallopian tube consists of one layer of simple columnar epithelium, which appears to be pseudo-stratified. Of these simple columnar cells, 25 % are ciliated columnar cells (Fig. 2), 60 % are secretory cells and less than 10 % are intercalated cells [5, 6].

The ciliated cells are mainly found on the apex of the mucosal folds [7], mostly in the fimbria (over 50 %) and less commonly in the isthmus (less than 35 %) [5, 6, 8]. Cilia extend from the apical surface of the ciliated cells into the lumen of the tube and are about 10 μm long and 0.25 μm in diameter [9]. Secretory cells are non-ciliated cells and contain apical granules that produce the tubular fluid. The least common cell type are intercalated cells, also known as peg cells whose function and even existence as a discrete cell type is a matter of debate. While some authors consider them a distinct type of secretory cells whose contents have been extruded with resulting collapsed cytoplasm [10], others consider them as merely representing a morphological variant of the classic secretory cells [11, 12]. Tubal epithelium undergoes cyclical changes in response to ovarian steroids which can be evident as a higher percentage of ciliated cells in the follicular phase, with gradual transition into a secretory cell-dominant pattern in the luteal phase of the cycle [10, 12]. The smooth muscle layer of oviduct has 3 layers: the innermost muscle cells are obliquely arranged, the middle layer is circularly arranged and the outer layer is oriented longitudinally [4]. The serosa of the tube is of mesothelial origin and is part of the visceral peritoneum.

Fig. 1 Illustration of the human fallopian tube, showing the longitudinal folds in cross-section at the (a) infundibulum, (b) ampulla and (c) isthmus. (with kind permission from Oxford University Press [3])

Tubal vasculature, lymphatics and innervations

Both uterine and ovarian arteries contribute to tubal blood supply, although their relative contribution in different individuals is subject to variability (Fig. 3). As a general rule, branches of ovarian artery supply the lateral part of the tube while branches of the uterine artery deliver arterial blood to the medial half of the tube. Similar to most other organs, venous drainage follows the arterial supply. Lymphatic drainage of the fallopian tube is similar to that of the ovary and terminates in the para-aortic nodes [2].

Both sympathetic and parasympathetic arms of the autonomic nervous system innervate the fallopian tube [14–16]. The sympathetic fibers are part of the inferior mesenteric plexus and are mainly found in the isthmic region of the tube. The afferent pain fibers travel along the sympathetic fibers and transmit their signals to T11–L2 section of the spinal cord. Parasympathetic innervation of the oviduct arises from S2–S4

Fig. 2 Scanning electron microscopic photograph of ciliated and secretory cells within the human fallopian tube epithelium. (with kind permission from Oxford University Press [3])

Fig. 3 Gross anatomy and vasculature of the tube. (With kind permission from McGraw-Hill, figure adopted from Williams Obstetrics 23rd edition [13])

through the pelvic plexus [14, 15]. However, it has to be mentioned that compared to the adrenergic supply, tubal cholinergic innervation is negligible [14].

Physiology of tubal transport: ciliary motility, muscular contractility and tubal fluid

The oviduct is not merely a passive conduit for the sperm, eggs and embryo transport [3]. In addition to its better known function in mechanical transport of gametes and embryo, some of its other roles include capacitation and storage of sperm, capturing the oocyte after ovulation, and maintaining and controlling migration of spermatozoa to the fertilization site. It also provides an optimized environment for fertilization; it nourishes the early embryo while it is carried to the uterus and amplifies signals from the embryo to the mother, contributing to early stages of embryo development [17]. Due to presence of restrictive ethical and technical issues, investigating details of gametes and embryo transport in human is extremely challenging. Having said that, employing explants of normal fallopian tubes from women undergoing salpingectomy and/or hysterectomy for various reasons, investigators have been able to shed some light on this elusive process. A multitude of factors, including endocrine signals, autonomic nervous input and cues from the embryo itself are thought to contribute to fine-tuning of this delicate process that will ultimately be executed with variable contributions from ciliary activity, muscular contractility and tubal fluid

flow [3, 17] and in this review we aim to elaborate on these three major effectors of tubal transport.

Ciliary motility

Ciliary structure

At the core of the ciliary ultrastructure lies a longitudinal bundle of microtubules, known as the axoneme (Fig. 4). In the fallopian tube, similar to other motile cilia, these microtubules are arranged in a 9+2 pattern in which nine outer/peripheral microtubule doublets surround a core of two inner/central single microtubules [9, 18, 19]. Each doublet microtubule consists of an A and a B microtubule, which are each 200 Å in diameter. Extending from each A microtubule to the B microtubule of the adjacent doublet, is a dynein arm; these dynein arms, depending on whether they anchor to the inner or outer side of the A microtubule, are called inner dynein arm (IDA) or outer dynein arm (ODA), respectively [9, 18, 19]. Dyneins are large polymeric proteins that are composed of a variable number of heavy, intermediate and light chains. Morphologically, these proteins can be described as a globular head followed by a stalk that comprises the stem and tail (or base) [19, 20]. The energy required for ciliary movement is derived from ATP hydrolysis through the ATPase activity of outer dynein arms. More specifically, ATP hydrolysis results in a conformational change in a motor domain of the protein and subsequently with the assistance of accessory structural motifs, the chemical energy from ATP

Fig. 4 Schematic diagram of a cross-section of a cilium. (with kind permission from Oxford University Press [3])

hydrolysis is transformed into a mechanical movement. This mechanical movement propels the attachment site of the ODA on the adjacent B microtubule towards the base of the axoneme (or cilia). Following the return of the ODA to its original conformation, the adjacent B microtubule (and the whole doublet to which it belongs) is pushed upward towards the tip of the axoneme. These sliding movements between adjacent peripheral doublets are transmitted through a different ultrastructural component, called radial spokes, to the central part of the axoneme, resulting in ciliary bending [21]. In addition to ATP, calcium is also required for ciliary motility as demonstrated by studies witnessing cessation of ciliary movements in the absence of calcium [22]. The exact mechanism by which ciliary bending pattern and direction is determined is not well understood. It has been suggested that the IDA is involved in regulation of ciliary bending pattern. Furthermore, the specific architectural distribution of ODA over the length of the axoneme may play a role in establishing the orientation of ciliary bending [23]. It is noteworthy that the 9+2 arrangement in ciliated epithelial cells is in contrast with the 9+0 arrangement of the single primary cilium that may be observed on the apical surface of secretory cells. These primary immotile cilia do not have dynein arms or nexin links and lack the central two single microtubules [24–27].

Regulation of ciliary beat frequency (CBF)

Various hormonal and neuronal factors have been shown to modulate the ciliary activity as shown by changes in ciliary beat frequency (CBF) in the fallopian tube. Various investigators have used different techniques to measure ciliary beat frequency in the fallopian tube among which the most commonly applied method is light intensity scatter measurement by phase-contrast high-speed digital microscopy [28, 29].

However, considering significant variations among these methods, direct comparison between the results of these studies is not always prudent.

Adrenergic and cholinergic stimulation

Both sympathetic and parasympathetic systems innervate the fallopian tube. Employing a culture system of ciliated epithelial cells of rabbit trachea, it was shown that beta adrenergic stimulation increases ciliary beat frequency and this effect can be reversed by using a beta adrenergic receptor blocker, propranolol [30]. This adrenergic stimulatory effect is probably subject to modulation by other factors as exemplified by the ability of IL-8 to block the stimulatory effects of isoproterenol in a bovine model [31]. Based on a murine knockout model in which muscarinic receptors are deficient, it appears that cholinergic system does not have any effect on CBF in the oviduct [32]. Pharmacological inhibition of cholinergic receptors in the wild type mice has revealed similar results [32]. This is in contrast with the effects of cholinergic system in the trachea [33] and prompts caution before extrapolating data from the cilia of the respiratory tract for the ciliated epithelium of the oviduct.

Despite the fact that cholinergic innervation of the fallopian tube is minimal, there is evidence to suggest that cholinergic stimulation of the oviduct exerts a contractile effect on the isthmus portion of the tube through type 3 muscarinic receptors (M3) [34]. The significance of M3 receptor is further established by demonstration of its requirement for the ACh-mediated calcium influx [35].

Angiotensin system

The presence of angiotensin II receptors in the tubal epithelium has been demonstrated by immunohistochemistry. The straining is more prominent during the follicular phase of the

ovarian cycle and is more present in the ampullary segment. Of note, tubal specimens obtained from menopausal women, display negligible staining for angiotensin II receptors. Furthermore, it has been demonstrated that angiotensin II can stimulate ciliary beat frequency, an effect that can be blocked by losartan, an angiotensin II receptor antagonist [36]. Viewing from a different perspective, the presence of angiotensin II, as well other components of the rennin-angiotensin system in various parts of the male reproductive tract such as the testis, vas deferens, prostate [37] and seminal fluid [38] raises legitimate questions about the possible interplay between male-produced angiotensin II and its cognate receptors in the female oviductal epithelium, the biological significance of which has not been determined but it clearly needs additional investigation.

Prostaglandins, Platelet Activating Factor (PAF) and tubal fluid viscosity

Early studies in 1980s had shown that PGE2 and PGF2 α both increase ciliary beat frequency in the fimbrial region of the rabbit oviduct [39]. This effect was postulated to be due to an increase in intracellular calcium concentrations [22]. Subsequent studies have demonstrated that other mediators, such as Platelet Activating Factor (PAF) may exert their stimulatory effect on CBF through an increase in PGE2 [40]. Changes in fluid viscosity has been linked to CBF with the teleologically explained aim of maintaining a constant level of CBF in the face of varying degrees of luminal fluid viscosity and it has been shown that the transient receptor potential vanilloid 4 (TRPV4) channel is involved in transmitting these extracellular signals to the intracellular ciliary apparatus [41].

Ovarian steroids

Specific endocrine profiles at different stages of menstrual cycle exert differential effects on ciliary beat frequency of the fallopian tube [42]. Due to the presence of a countercurrent exchange system between the ovarian and fallopian tube vasculature, the oviduct is exposed to much higher concentrations of ovarian steroids as compared to the systemic circulation [43].

Moreover, following Graafian follicle rupture and ovulation, follicular fluid, which is rich in ovarian steroids and other bioactive substances, comes into direct contact with tubal epithelium.

In vitro studies using human fallopian tube explants have shown that estradiol by itself at 10 μ M concentrations does not have any tangible effect on ciliary beat frequency [44]. However, another study has shown a small but progressive increase in CBF during the follicular phase of the cycle in guinea-pig, concomitant with rising levels of estradiol [45].

In the immediate period after ovulation, there is a major increase in CBF [46]. This has been attributed to the effects of

progesterone in an estrogen-rich milieu [14]. This observation is further supported by experiments demonstrating that pre-ovulatory follicular fluid obtained from women undergoing IVF treatment at the time of oocyte retrieval, causes a significant increase in CBF [3]. However, in vitro studies show that high dose progesterone can inhibit CBF [44, 47]. This effect can be reversed by the use of mifepristone, a progesterone receptor antagonist [44]. One possible explanation for this discrepancy regarding the effects of progesterone in the secretory phase could be the dominant stimulatory effects of other constituents of follicular fluid such as prostaglandins.

This is consistent with studies in guinea-pig that have shown an increase in CBF during the early luteal phase, followed by a decrease in mid-luteal phase when progesterone concentration is maximal. Subsequently, in late luteal phase and concomitant with the fall in progesterone levels, CBF rises again to levels seen in follicular phase [45].

Similar to antagonistic effects of estrogen and progesterone towards each other at the endometrial level, it has been suggested that their effects on CBF in the fallopian tube may be nullifying [48]. Considering that the effect of progesterone on ciliated cells is very rapid, it has been suggested that these effects are part of the non-genomic actions of progesterone [49].

Both classic (cytoplasmic) progesterone receptors [50], as well as membrane-bound progesterone receptor gamma [51] have been implicated to be involved in signal transduction to ciliated cells.

Adrenomedullin

Adrenomedullin (ADM) is a peptide hormone belonging to the calcitonin/calcitonin-gene-related peptide (CGRP) family and has been found to be expressed in both mouse and human oviduct. Its expression is more pronounced in the isthmus region of the tube and it has been shown to increase CBF in a dose-dependent fashion [52]. Furthermore, the local expression of ADM in the oviduct has been linked to the steroid environment with its peak observed in early luteal phase. Sperm contact is another factor that seems to enhance the expression of ADM [52]. Stimulating effects of ADM is blocked by the calcitonin-gene-related peptide (CGRP) receptor antagonist [53]. In line with these studies, it has been suggested that plasma and tubal levels of ADM are lower in patients with tubal ectopic pregnancy compared to those with a normal pregnancy [54].

Role of CBF in gamete and embryo transport

Based on several different lines of evidence, ciliary activity plays a major role in tubal transport of gametes and embryos.

In the absence of muscular contractility following administration of isoproterenol in the rat oviductal ampulla, tubal transport of surrogate ova and their accompanying COC was unaffected implying that the cilia alone are adequate for transporting the ovum [55].

Additional evidence for the important role of ciliary function in tubal transport stems from the observation of subfertility in women with Primary Ciliary Dyskinesia, also known as Immotile Cilia Syndrome [56, 57]. Although there have been case reports of normal pregnancy in some of these patients [58, 59], this could very well be due to either some residual ciliary function in these patients or a different and tissue-specific pattern of disease phenotype in the reproductive and respiratory tracts based on the specific causative mutation(s) [60].

Muscular contractility

Two major types of muscular contractions have been recognized in the myosalpinx: continuous tonic contractions and short-lived but frequent periodic contractions [61, 62].

Continued tonic contractions most likely work as a functional gate at the uterotubal junction (UTJ) and ampullary-isthmic junction (AIJ) and will only allow the passage of gametes and embryos when optimal condition on the other side has been established i.e. endometrial receptivity for the developing embryo and prime fertilization condition for spermatozoa [63]. The transient embryo's pause behind the AIJ will come to an end once progesterone effects become maximal in mid luteal phase with its resultant down regulation of the alpha adrenergic receptors and relaxation of the isthmic muscle tone [64]. Regarding the sperm transport, it has been shown that if sperm stays freely floating in the ampulla of the tube, the chances of polyspermy will increase [65–67]. The isthmus portion of the tube and AIJ will therefore, prevent polyspermy by limiting the rate of the sperm release into the ampulla [3]. On the other hand, the brief periodic contractions do not have a major role in propelling the tubal contents and it is believed that their major role is to provide an adequately mixed floating medium of tubal secretions for the gametes and embryo [68]. An additional role for the muscular activity has been implicated in the oocyte pick-up process; during this process, the fimbrial end of the tube, that has come in close proximity to the rupturing follicle through the muscular activity of the mesosalpinx, demonstrates a series of oscillating activity which is believed to be responsible for the oocyte retrieval after its release [69].

Tubal fluid

Secretory epithelium of the tube is actively involved in secretion of a variety of bioactive compounds [70]. Compared to

the plasma, human tubal fluid is very rich in potassium and bicarbonate and has very high concentration of arginine, alanine and glutamate [71]. Its glucose concentration varies according to the stage of the menstrual cycle and drops significantly around the time of ovulation [72]. Maximal production of tubal fluid is seen in midcycle and it is believed that its constituents, mainly prostaglandins, play a major role in modulating myosalpingeal contractile activity in order to facilitate the ovum pick up and embryo transfer [72–74]. Another specific feature of tubal fluid is the presence of oviduct-specific glycoproteins with their highest levels observed in the peri-ovulatory phase. Using radiolabelled L-[35S] methionine and [3H]glucosamine, investigators have been able to identify and isolate two proteins, named Tubal Epithelial Protein 1 and 2 (TEP-1 and TEP-2) that were exclusively produced by the tubal explants from premenopausal women and were absent in similar explants' secretions from postmenopausal women [75, 76]. Although the biological role of these proteins is not well established, it has been suggested that their production and secretion is enhanced in response to estrogenic stimulation [77]. At midcycle, following follicular rupture and ovulation, follicular fluid becomes the major component of the tubal fluid immediately after ovulation. In addition to the modulatory effects that follicular fluid exerts on CBF and tubal muscular contractility, the simple stream of follicular fluid into the tubal lumen may assist the ovum pick up and transport process [17].

Pathophysiology of tubal transport: ciliary dysfunction and reproductive failure

In this section, pathological states in which tubal transport may be adversely affected will be discussed. It is noteworthy to mention that routinely performed clinical diagnostic tests for tubal disease such as hysterosalpingography (HSG) or laparoscopic chromo-pertubation, can only establish the anatomic patency of the tube and are not capable to evaluate any other aspect of tubal physiology whose functional integrity is clearly required for establishment of a successful pregnancy.

Endometriosis

The association between endometriosis and infertility is firmly established in the literature; however, the causative mechanism(s) has (have) not been fully elucidated, particularly in the setting of mild endometriosis where anatomic distortion of the pelvic cavity is less pronounced, if at all present. Numerous studies in the past several years have shown that the biochemical signature of peritoneal fluid in patients with endometriosis is more pro-inflammatory compared to healthy women [78]. In women affected with endometriosis, activated macrophages in the peritoneal cavity are more abundant compared

to their healthy counterparts [79–81]. Peritoneal fluid of women with this condition imposes a significant inhibitory effect on ciliary beat frequency [82]. Factors in the peritoneal fluid that are responsible for this detrimental effect on CBF are unclear. One candidate, IL-6, has been shown to significantly inhibit CBF at concentrations of 1 ng/mL, an effect that can be reversed by administration of an IL-6 blocking antibody [83]. Another possible mechanism linking endometriosis to infertility is defective interactions between the sperm and the fallopian tube epithelium in women with endometriosis [84]. Furthermore, endometriosis can cause infertility through tubal damage that ensues development of Salpingitis Isthmica Nodosa (SIN) and intramucosal endometriosis [85]. One prospective study has found up to 24 % unilateral and 76 % bilateral SIN in a cohort of 87 patients with laparoscopically –proven endometriosis [86], which is significantly higher than reported incidence of 0.6–11 % in the general population [87].

In addition, some investigators have suggested that the dominance of proinflammatory cytokines in peritoneal and tubal fluid in women with endometriosis may have an adverse effect on oocyte quality and/or embryo development [88, 89]. At a clinical level, this hypothesis is further supported by studies demonstrating a decreased pregnancy rates when IVF-ET treatment is performed using donated oocytes obtained from women with endometriosis as compared to when oocyte donors did not have endometriosis [90]. Regardless of the causative factor(s) that are responsible for the adverse effects of endometriosis on fertility, surgical treatment of stage I and II endometriosis has been demonstrated to result in a clinically small, but statistically significant, improvement in spontaneous conception following surgery [91, 92]. This clinical observation can probably be considered as yet another evidence to implicate endometriosis in subfertility [93].

While it is certainly biologically plausible and clinically documented that tubal disease and scarring due to any underlying condition such as infection, previous tubal surgery or severe endometriosis predisposes to ectopic pregnancy [94], the evidence is less clear for the possible association of milder forms of endometriosis and tubal ectopic pregnancy. Although some studies have not found an association [95], others have alluded to endometriosis as a possible contributing factor for the occurrence of ectopic pregnancies with implicated pathophysiological mechanisms such as abnormal ciliary beat frequency or abnormal tubal peristalsis [96–98].

Smoking

There has been a well-established association between increased risk of ectopic pregnancy and tubal infertility in smokers. There is a fourfold increase in risk of ectopic pregnancy among women who smoke more than 20 cigarettes a day [99, 100].

Nicotine has also been shown to alter tubal motility and decrease tubal blood flow [101, 102]. Animal studies show that incubation with dissolved mainstream (MS) or sidestream (SS) cigarette smoke causes a dose-dependent decrease in ciliary beat frequency, an effect that is reversible after a washout period [103]. Tobacco smoking can also exert a detrimental effect on oocyte retrieval by the tubal fimbriae, independent of its inhibitory effects on CBF. This effect has been attributed to detachments of the connections linking the ciliated epithelium and the oocyte [104]. Moreover, though some authors have suggested that chronic tobacco exposure does not have a measurable effect on the number of ciliated cells or expression of ciliogenesis-specific transcription factors studied in human fallopian tube specimens obtained at the time of tubal sterilization [105], others have demonstrated a reduction in the number of ciliated cells and ciliogenesis in the tubal epithelium following exposure to tobacco smoke [106].

Effects of microorganisms on the fallopian tube: *Neisseria gonorrhea* and *Chlamydia trachomatis*

The association between Pelvic Inflammatory Disease (PID) and development of hydrosalpinx and/or pyosalpinx with its devastating effects on tubal anatomy and resultant tubal infertility is well known. However, even milder forms of infectious salpingitis have been implicated in tubal-factor infertility [107, 108].

Gonococcal endotoxin can reduce ciliary activity and subsequently affect fertility. This microorganism can also attack and destroy the non-ciliated cells of the tubal mucosa. The ensuing tissue damage stimulates the mucosa to regenerate and in the process significant amounts of proinflammatory cytokines, such as tumor necrosis factor (TNF) α are secreted into the tubal lumen [109, 110]. It has been suggested that production of these pro-inflammatory cytokines, may be the mechanism by which damage to the oviduct occurs [111–113].

Chlamydia trachomatis is another common sexually transmitted infection that has been linked to fallopian tube injury, and consequently tubal infertility and ectopic pregnancy [107, 108].

Chlamydia can cause a direct toxic effect on the mucosal cells of the fallopian tube, causing the oviduct to lose its microvilli and cell attachments. This will eventually lead to permanent tubal tissue damage and scarring [114]. Chlamydial infection can affect oviductal smooth muscle and destroy its spontaneous contractile activity which will ultimately result in stasis and retention of the oviduct secretions, hydro/pyosalpinx formation and infertility [115].

A chlamydial protein, hsp60, has been suggested to be the mediator of detrimental effects of *chlamydia* on tubal function [116–118]. Chlamydial hsp60 can trigger both a humoral and cell-mediated immune response [119]. Subsequently, recruited and activated macrophages secrete a number of

inflammatory cytokines, such as TNF α , interleukin-1 β and interferon γ and cause tissue damage [120–122].

HPS60 also upregulates the expression of matrix metalloproteinases, which can cause scarring due to enhanced remodeling of the extracellular matrix [119, 123]. Certain serotypes of Chlamydia such as serotypes C and E can have a particularly pronounced inhibitory effect on CBF [124] and may confer a grim prognosis for future fertility.

Other microorganisms have also been shown to incur tubal damage and tubal infertility. Animal studies show that *Escherichia Coli* can result in deciliation, shortening of the ciliary cells and loss of microvilli of the secretory cells [125].

Conclusion

Spontaneous conception requires remarkably coordinated and tightly regulated transport of gametes and embryo(s) through the fallopian tubes, during which significant physiological milestones such as sperm capacitation, oocyte fertilization and initial embryonic development are achieved. These processes require not only anatomically patent tubes, but also normal function of the tubal epithelium and tubal fluid. At present, clinically available diagnostic tests only attest to the patency of the fallopian tubes and are not capable to further assess the tubal function. A better understanding of the molecular basis of tubal physiology may help in development of more robust and specific diagnostic test(s) to better elucidate the role of tubal disease in infertility and other adverse reproductive outcomes.

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