Chapter 21
What are the seminal vesicles?
Development, secretions and functions

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Seminal vesicle structure and function

The seminal vesicles, along with the prostate and bulbourethral glands, are accessory sex glands that are found only in males (Fig. 1). These bilateral glands are comma-shaped structures located between the bladder and the rectum that in men are each 5-7 cm long when uncoiled, with a volume of approximately 13 ml. Each seminal vesicle consists of one long highly infolded sac lined with a single cell layer of pseudostratified secretory epithelium atop a discontinuous layer of basal cells and a thick outer layer of smooth muscle cells innervated by sacral nerves S2-S4 (Fig. 2). The extensive infoldings of the seminal vesicle epithelium maximize the epithelial surface area and secretory capacity of the organ.

The main function of the seminal vesicles is to produce a complex fluid that is incorporated into the ejaculate and facilitates various aspects of the subsequent process of fertilization. Seminal vesicle secretions are stored within the gland as a viscous fluid until they are expelled at the time of orgasm. The seminal vesicle fluid is expelled through a single duct at the time of orgasm, where it mixes with other components of the developing ejaculate, as described in detail below.

Role of androgen signaling in seminal vesicle development and function

Seminal vesicles are derived from the Wolffian ducts of the male fetus, which are paired embryonic structures that also give rise to the epididymis and ductus deferens. The seminal vesicles originate from the most caudal portion of the Wolffian ducts, near where these bilateral ducts juncture with the fetal urogenital sinus. Initial masculinization of the fetal reproductive tract and the differentiation of the epididymis, ductus deferens, seminal vesicles, prostate and bulbourethral glands in the male occurs in response to androgens

secreted by fetal Leydig cells in the testis. Mammalian embryos are initially ambisexual, and Wolffian ducts initially develop in the female embryo as well. However, in the absence of exposure to amounts of androgen sufficient to cause the stabilization and development of the Wolffian ducts, such as occurs in the male embryo, the female Wolffian ducts regress.

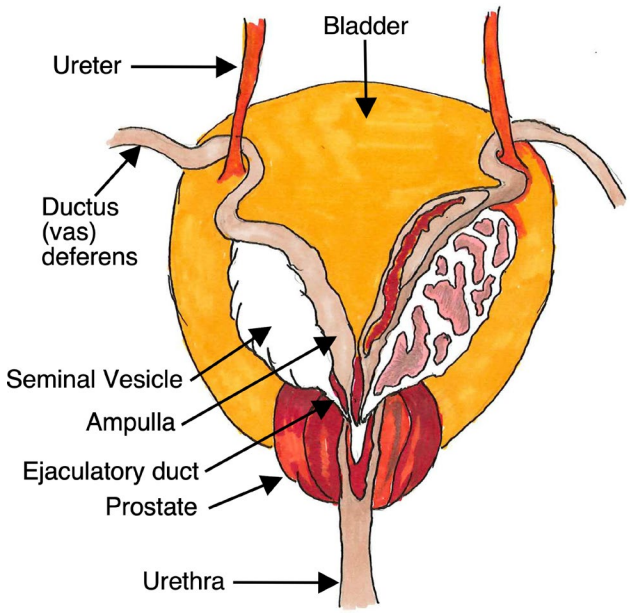

Figure 1. Posterior view of human urogenital organs including seminal vesicles, bladder, urethra, prostate and ejaculatory ducts. Intact organs are shown on the left. Internal structures of the organs and the formation of the ejaculatory duct are shown in the central region and on the right.

Following their fetal differentiation, the seminal vesicles and the other accessory sex organs in the male remain immature until the time of puberty. This pre-pubertal interval in various species is highly variable, ranging from a few weeks in mice to over a decade

in humans. Increasing androgen concentrations during puberty induce rapid growth, morphogenesis and secretory function of the seminal vesicles. These glands are obligatarily dependent on androgen not only for pubertal development but also for maintenance of their adult function and secretory capabilities. Loss of androgen signaling by castration or other treatments that block normal androgen signaling (e.g., anti-androgens) induces a striking and rapid involution of these structures and abolishes their secretory activity at any age in the adult mammal.

Androgen receptors (ARs) are essential for seminal vesicle organogenesis, as demonstrated by studies showing that transgenic mice lacking AR do not develop seminal vesicles. The AR present in the Wolffian duct, as well as other fetal structures such as the urogenital sinus that forms other accessory glands, function as ligand-activated transcription factors that stimulate the initial development and morphogenesis of the seminal vesicles.

Development of urogenital organs such as seminal vesicles and prostate involves reciprocal mesenchymal-epithelial interactions. Androgen receptors are present initially in the mesenchyme, but not the epithelium, of fetal organs such as Wolffian ducts and urogenital sinus. Androgen acts to stimulate seminal vesicle epithelial development indirectly through AR in the mesenchyme, and then the mesenchymal cells drive epithelial development and proliferation through mechanisms that still remain unclear.

Adult seminal vesicles express AR and estrogen receptors (ESR1, ESR2) in stromal, smooth muscle and epithelial cells, and various transgenic models have been developed to demonstrate unique roles of AR in various cell types such as the seminal vesicle smooth muscle. For example, seminal vesicles lacking smooth muscle AR were 55% smaller than normal. Proximal epithelial cells were low and cuboidal with little cytoplasm indicating that testosterone-derived signals from smooth muscle cells are important for maintaining normal epithelial cell function including secretion. In adults, the epithelial layer was less folded, and the stromal smooth muscle layer depth was reduced about 50% and disorganized. The numbers of copulatory plugs were similar to normal 4 h after coitus but were smaller with a soft and fibrous consistency that likely is responsible for the 70% decrease in plug-positive females when assessed the morning after coitus. In vivo fertilization was reduced by more than 60% and in vitro fertilization was reduced at low sperm concentrations, perhaps due to a mild defect in sperm binding to the zona pellucida.

Androgen signaling in smooth muscle may also serve to limit epithelial cell proliferation, as the number of epithelial cells undergoing mitosis in mice lacking AR in seminal vesicle smooth muscle cells was increased 3-fold, resulting in hyperplasia. Elevating estradiol (E_2) while keeping testosterone levels constant also increased epithelial cell proliferation by more than 2-fold. Increased E_2 did not alter epithelial cell height suggesting no regulation of epithelial cell differentiation, but the depth of the smooth muscle layer was increased indicating that E_2 supports smooth muscle proliferation.

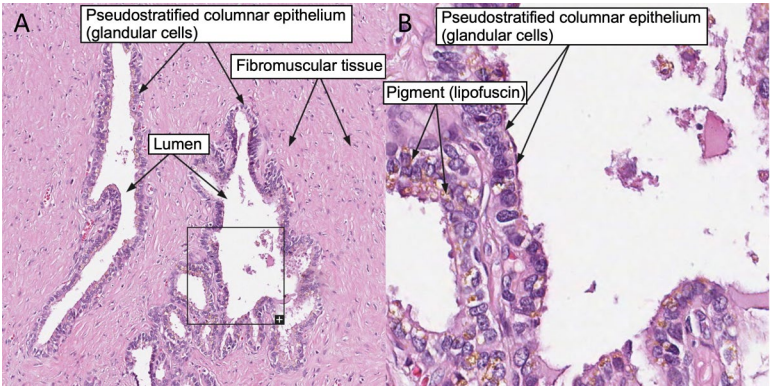

Figure 2. A) low power view of a cross section of seminal vesicle showing fibromuscular tissue surrounding pseudostratified columnar epithelia and **B)** a higher magnification view of the region within the box in A showing the single layer of epithelial cells. From Pontén F, Jirström K, Uhlen M. The Human Protein Atlas-a tool for pathology. J Pathol. 2008 216(4):387-93.

Release of seminal vesicle fluid into the ejaculate at the time of orgasm

The seminal vesicle mucosa is surrounded by extensive tunics of smooth muscle that can propel the seminal vesicle secretion into the urethra at the time of ejaculation, and release of seminal vesicle fluid at the time of ejaculation is partially due to the contraction of the smooth muscle elements in the seminal vesicles themselves. In addition, contraction of a number of striated muscles in the urogenital region also facilitate the expulsion of seminal vesicle fluid

as well as that from other glands such as the prostate and is critical for progression of the ejaculate through the male reproductive tract.

Release of seminal vesicle fluid is coordinated with that of the other components of the ejaculate to insure near-simultaneous expulsion of all of the components that comprise the seminal fluid. Sympathetic discharge at orgasm causes vigorous contraction of the seminal vesicles and the rapid movement of the seminal vesicle fluid through the excretory duct of the seminal vesicles. Simultaneously, sperm and associated fluid originating from the testis and epididymis are conveyed down the ductus deferens. The seminal vesicle excretory duct merges with the distal ductus deferens to form the ejaculatory duct that empties into the urethra where it passes through the prostate (Fig. 1). Secretions from the prostate are then added to the developing ejaculate, and finally bulbourethral gland secretions are added at the base of the penis to complete the ejaculate that then passes into the female reproductive tract.

Although many organs contribute components to the final ejaculate, seminal vesicles provide a major portion of the ejaculate volume. The exact amount of the semen volume that originates from the seminal vesicles varies in different animals, but studies using a variety of species and various methods of measuring the contribution of the seminal vesicle fluid to the ejaculate suggest that seminal vesicle secretion is the major constituent of the ejaculate and makes up more than half of the ejaculate volume in humans as well as the other animals studied.

Role of the seminal vesicle in clotting of seminal fluid

In species such as rats, mice and some non-human primates, the seminal fluid forms a copulatory plug following its deposition in the vagina. These copulatory plugs in species such as rodents inhibit leakage of seminal fluid from the vagina, and the plugs in rodents are gelatinous and durable. Copulatory plugs in rodents can be detected many hours after a successful mating, and function as a reliable record of successful copulation in these species.

Copulatory plugs are formed in the female reproductive tract due to clotting proteins derived from the seminal vesicle fluid associating with enzymes from the prostate. Human semenogelin I and II (corresponding to seminal vesicle secretion proteins SVS2-SVS6 in mice), the main components of the fibrous coagulum, are secreted from seminal vesicles. Like rodent semen, human semen

also coagulates after ejaculation. However, in striking contrast to rodents, which form long-lasting and resilient copulatory plugs, following clotting human semen will liquify within a few minutes due to cleavage of semenogelin by prostate-specific antigen, a chymotrypsin-like prostatic protease. Coagulation allows sperm to be coated with nutrients and factors that contribute to fertilization. Subsequent liquefaction permits sperm to swim into the cervix and uterus (Chapter 25).

Seminal vesicle fluid components and activities

Seminal vesicle fluid is a slightly alkaline secretion that is highly viscous and contains fructose, which serves as an immediate energy substrate for ejaculated sperm to support their motility. Low levels of fructose in semen are an indicator of seminal vesicle obstruction or dysfunction. Seminal vesicles also produce citric acid, which modulates pH and metabolism. In addition, the seminal vesicle secretes semenogelin/SVS proteins, metallothionein-1 (Mt-1), and transglutaminase-4 (TGM4). Aquaporins present in the apical and basolateral membranes of seminal vesicle secretory cells regulate water transport contributing to high concentrations of proteins (up to 200 mg/ml) and the viscosity of seminal vesicle fluid. Expression of aquaporins in seminal vesicles (and prostate) is dependent on testosterone as castration decreases the levels of at least 5 aquaporin proteins in rats.

Seminal vesicle-derived prostaglandins in semen increase female genital tract smooth muscle contractions to aid in sperm transport. Seminal vesicles also secrete various ions, enzymes, and the proteins involved in the clotting process of the semen after ejaculation. Reactive oxygen species (ROS) scavengers including superoxide dismutase, catalase glutathione peroxidase/reductase, ascorbic acid, uric acid and thiols are produced to counteract elevated levels of ROS and oxidative stress that are associated with decreased sperm motility and sperm-oocyte fusion. Seminal vesicle secretions facilitate fertilization, and a number of studies have shown that the fertility of rodents with their seminal vesicles removed is reduced, but not eliminated.

Seminal vesicles are somewhat unique among the accessory sex organs in that they are species variable. Some groups of animals such as carnivores, e.g., cats, and cetaceans, e.g., whales, lack seminal vesicles. The data in species such as rodents showing diminished fertility in the absence of the seminal vesicles suggests that the lack

of the seminal vesicles would be expected to inhibit fertility, but these species that have lost their seminal vesicles during their evolution may have other methods of compensating for the loss of seminal vesicle fluid and its normal supporting role in fertilization.

Clinical relevance of the seminal vesicles

The accessory sex organs in general have important medical significance due to the prevalence of two major prostate diseases in men that are of immense clinical importance, benign prostatic hyperplasia (BPH), which afflicts 80% of men 70 years of age and older, and prostatic cancer, which is the second most common neoplasia in men. Although BPH also occurs in the dog as well as human, this disease does not naturally occur in other species. The reasons for this are unknown.

Despite the extensive similarities between the prostate and seminal vesicles in terms of anatomical location, secretory function and hormonal regulation, clinical problems involving the seminal vesicles are rare. Seminal vesiculitis can occur as a result of bacterial infections arising from surgery or sexually transmitted diseases, but the incidence of this is very low. Seminal seminal vesicle cancer is exceedingly rare, with only about 60 cases described in the literature, and no other common clinically significant problems related to seminal vesicles occur. The reason that these two organs, which share extensive developmental and functional similarities, are totally different in terms of their susceptibility to pathological changes has been speculated on for decades but remains unknown despite the clinical importance of the question.

Suggested reading

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