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Features of Sperm Development: Spermatogenesis and Fertilization

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Annotation: Spermatozoa are highly specialized cells that are not capable of growth and division. The sperm consists of a head containing the paternal genetic material (DNA) and a tail that ensures its mobility. In the presence of a large nucleus, the sperm has practically no cytoplasm, the presence of which is characteristic of most cells of the body. The morphological heterogeneity of each man's ejaculate is unique.

Keywords: spermatozoon; spermatogenesis; capacitation; acrosome; fertilization; infertility.

Spermatozoa have a complex and poorly understood life cycle. The process of differentiation of spermatogonies into spermatozoa is called spermatogenesis. It is carried out through both mitotic and meiotic division, as well as intensive cellular remodeling. There are 4 stages of spermatogenesis: growth, reproduction, maturation, and formation. Spermatogenesis provides the production of genetic material necessary for reproduction. Meiosis provides genetic diversity. Before acquiring the ability to fertilize an egg, spermatozoa undergo a series of cellular or physiological changes, including capacitation and acrosomal reaction. In humans, the maturation phase of spermatocytes takes 25.3 days, and the formation phase (spermiogenesis) takes 21.6 days, the total duration of spermatogenesis is approximately 74 days. Spermatogenesis is supported by various internal and external regulatory mechanisms. Before acquiring the ability to fertilize an egg, spermatozoa undergo a series of cellular or physiological changes, including capacitation and acrosomal reaction. Although spermatozoa remain viable in the genital ducts of the male body for many weeks, once they enter the genital tract of the female body, they can survive for a short period of time, not exceeding 24-48 hours at body temperature. However, with a decrease in temperature, sperm can persist for several weeks.

At the moment, it is especially important to conduct a detailed characterization of disorders that occur during the main stages of the sperm life cycle and identify their impact on fertility function.

As is known, changes in the structure of spermatozoa are an important factor leading to impaired fertility in men, up to 7% of whom experience problems with conception due to functional

disorders of gametes [1].

In the embryonic period, the primary germ cells are populated in the embryo of the testicle, subsequently giving rise to male gametes.

The initial stage in the life cycle of spermatozoa is the most important process in human reproduction, during which highly specialized haploid cells (spermatozoa) are formed from undifferentiated cells with a diploid set of chromosomes (spermatogonia), called spermatogenesis. It begins during puberty and persists into old age [1]. The formation of spermatozoa occurs in the convoluted seminal tubules of the testicles in the following sequence of cellular forms: spermatogonia, spermatocytes of the first and second orders, spermatids, spermatozoa. As the germ cells mature, they gradually shift from the basement membrane to the lumen of the convoluted seminal tubules. Sertoli cells play an important role in the development of male gametes, which are connected to blocks of spermatogenic cells by processes and depressions. There is close contact between Sertoli cells, which forms a special histological barrier for the development of male germ cells, limiting them from the effects of the immune system [2]. Sertoli cells also phagocytize dead spermatogenic cells and secrete liquid into the lumen of the tubule, into which the spermatozoa are immersed after detaching from the spermatogenic epithelium.

Thus, Sertoli cells control the development of spermatozoa. On the periphery there are the youngest, undifferentiated germ cells – spermatogonia. Closer to the center and lumen of the tubule are spermatocytes of the first order, then there are spermatocytes of the second order, oval spermatids are located near the lumen, and mature spermatozoa are located in the tubule itself. In spermatogenesis, there are 4 stages: reproduction, growth, maturation and formation.

The stage of reproduction occurs by mitotic division of the initial stem cells (spermatogonia) with the formation of subsequent cell types of germinative cells. Spermatogonia make up only 0.03% of the cells of the spermatogenic series. Morphologically, there are two types of spermatogonia: A and B. In turn, type A spermatogonies differ in the degree of chromatin condensation into dark (condensed) and light (diffuse) cells [2; 3]. Dark spermatogonia are reserve stem cells and normally do not show proliferative activity. In the process of spermatogenesis, only light spermatogonies are divided, which are semi-stem cells and are capable of giving rise to type B spermatogonies, which, in turn, undergo several mitotic divisions, differentiating into spermatocytes of the first order. The growth stage consists in an increase in the size of spermatocytes of the first order in the order they pass the interphase of meiosis. The stage of maturation includes two consecutive divisions of meiosis. After the first division (reduction), two spermatocytes of the second order are formed from a spermatocyte of the first order. Prophase I of meiosis takes quite a long time, so the primary spermatocyte is the longest–lived. Secondary spermatocytes do not live long (on average 1.1–1.7 days). Secondary spermatocytes enter the second division of meiosis (equational), forming spermatids. Spermatocytes of the second order are twice as large, and spermatids are four times smaller in volume of spermatocytes of the first order [3].

In spermatogonies and spermatocytes of the first order, there is a diploid set of chromosomes (2n=46), in spermatids the number of chromosomes is haploid (n=23) [4]. The most difficult stage of formation, or spermiogenesis, which is characterized by the transformation of spermatids into spermatozoa. During the formation stage, the future sperm acquires its characteristic highly specific features.

At this stage, chromatin condensation occurs, which becomes genetically inert, and the movement of cell organelles is also observed [4]. So the Golgi apparatus shifts to the nucleus and forms an acrosome – a vacuole filled with proteolytic enzymes, the chemical composition of the plasma membrane changes. After displacement to the apical end of the cell, the centrioles move to the opposite pole and are located one closer to the nucleus, and the other more distally [5]. The proximal centriole will participate in the formation of the spindle of the first division during the crushing of the zygote, and a flagellum begins to form from the distal one, inside which an

axoneme is formed. Mitochondria are arranged in spirals around the base of the flagellum. In parallel with the described processes, gametes are released into the lumen of the tubule, during which Sertoli cells play an active role. They are able to make cellular movements as the spermatids move towards the lumen of the tubule. Spermatids originating from the same spermatogonies remain connected by bridges that facilitate the transport of cytoplasmic products. After the destruction of the intercellular bridges, mature spermatids detach from the spermatogenic epithelium and become free cells called spermatozoa. During release, fragments of the cytoplasm of Sertoli cells, called cytoplasmic droplets, may remain in the sperm. The detection of such droplets in gametes contained in sperm indicates their immaturity [6].

At the same time, there is evidence that spermatozoa that have never passed through the appendage of the testicle retain the ability to fertilize an egg in vitro [7]. The entire spermatogenesis takes about 64-72 days [2; 5]. The spermatozoa located in the testicle and its appendage are weakly mobile or completely motionless and, therefore, are unable to fertilize the egg. In the structure of the mature male germ cell, the head, neck and tail are isolated, its length is about 50-60 microns. The head of the sperm is oval in shape, it contains a nucleus surrounded by a thin layer of protoplasm. There is a modified centrosome in the neck, which after fertilization will play an important role in crushing the zygote. Characteristic parameters of a normal sperm are: an oval head 4-6 microns long and 2-4 microns wide, an acrosome occupies 40-60% of the head, there are no defects in the neck and tail, a cytoplasmic drop should not exceed the size of the head [3].

The tail is represented by protoplasm and is endowed with locomotor functions, primarily it provides movement along the female genital tract at a speed of about 2-3 mm/min. The longest part of the tail is the most important part of the movement apparatus. The nine coarse fibrils of the outer ring decrease in thickness and eventually disappear, leaving only the inner fibrils on the axial rod for almost the entire length of the main section. The fibrils of the Main part are surrounded by a fibrous membrane of the tail, consisting of branched and anastomosing semicircular strands held together by attaching to two strips stretching on both sides of the tail throughout its entire length. The conifer ends with an end section 4-10 microns long and less than 1 microns in diameter [8]. Such a small diameter is due to the absence of an outer fibrous membrane and distal thinning of microtubules. Normal spermatozoa are characterized by progressive translational motion with spiral rotation around their axis. The lack of sperm motility (asthenozoospermia) can be caused by disorders of the axoneme and microtubules [9].

There are two types of spermatozoa – carriers of sexual X and Y chromosomes, and the spermatozoa carrying the X chromosome differ in larger sizes [6]. Recent studies indicate an increase in the number of genetically determined forms of reproductive dysfunction in men, which are often associated with structural and quantitative karyotype abnormalities, microdeletions in the Y chromosome. Mutations of genes, for example, the CFTR gene, involved in spermatogenesis or the formation of the male reproductive system, are also in many cases the cause of fertility disorders.

Unlike most mammals, humans have the highest percentage of morphologically abnormal sperm [4; 8]. The main molecular disorders of spermatogenesis can be attributed to two different groups: changes in spermatid organelles that affect the further development of the sperm, and independent violations of the structure of the emerging sperm. An example of the pathologies of the first group: the cuff is a spermatid organelle, which is a cluster of microtubules surrounding the nucleus of the forming spermatid and consisting of tubulins and proteins associated with microtubules. The functions of the cuff include protein transport, as well as participation in the assembly of the tail and condensation of the nucleus of the spermatid. Microtubules, in particular, contain alpha-tubulin and beta-tubulin heterodimers, gamma-tubulin and keratin [2; 9].

Serious changes in the morphology of the cuff are observed in the case of mutation of the Restin protein (CLIP170), which consistently leads to impaired sperm development. For example, mice containing the mutant CLIP170 protein have spermatozoa with an abnormal head shape. Restin is

a cytoplasmic binding protein also involved in the regulation of tubulin dynamics [9].

As an illustration of the second group of pathologies, incorrect attachment of the sperm head to the neck can be distinguished, which is most often found due to a violation of the process of centriole divergence and occurs during early events of spermatogenesis, which makes spermatozoa practically non-fertile. With a decrease in the activity of proteasomes, the release of the centrosome is weakened and the formation of the centrosome after fertilization occurs, which ultimately leads to a violation of syngamy and the expulsion of the embryo [2; 5]. Evaluation of violations of the cytoskeleton of the tail and centrioles is still a poorly studied area of pathology of spermatogenesis, therefore, it is necessary to develop new experimental techniques that contribute to the study of these anomalies and, as a result, the development of a new class of drugs [6].

During ejaculation, from 2 to 5 ml of sperm is released, which contains from 60 to 200 million spermatozoa [6; 10]. During ejaculation, the spermatozoa that have emerged from the tail of the epididymis are mixed with the secretions of the accessory glands (seminal vesicles, prostate gland) in a certain sequence and acquire mobility. Sperm ejaculated during sexual intercourse consists of sperm and the liquid part, which is the secret of the mucous membrane of the seminal ducts (about 10% of the total), the prostate gland (about 30%) and seminal vesicles (almost 60%), which is released during ejaculation in the last place and serves to dilute sperm when passing through the ejaculatory duct and urethra. The spermatozoa of the first portion of the ejaculate are characterized by significantly better mobility and survival than the spermatozoa of subsequent portions [5; 7].

The second stage in the life cycle of a sperm can take place in the female body. During ejaculation, sperm is ejaculated into the area of the external opening of the cervical canal and the posterior arch of the vagina. At the same time, at this moment, spermatozoa do not yet have the fertilizing ability. This is achieved as a result of the process of capacitation under the influence of the secrets of the female genital tract.

Due to the high acidity of the vaginal contents (pH=4.0), most male gametes, including pathological ones, die at this time and are phagocytized [3; 11]. The remaining spermatozoa quickly penetrate the mucus, which is released from the cervical canal during sexual intercourse under the influence of contractions of the muscles of the cervix. The slightly alkaline reaction of cervical mucus contributes to an increase in the motor activity of spermatozoa [1; 4]. They penetrate through the cervical canal into her body at a rate of 3-4 mm per minute, after which they are dosed into the fallopian tubes. Prostaglandins contained in sperm activate the contractile activity of the myometrium and smooth muscle cells of the fallopian tubes, which is also important for the adequate promotion of gametes [7; 12]. Movements of the cilia of the epithelium of the fallopian tubes, as well as positive rheotaxis – the ability to move against the current of the secretion of the genital tract - play an essential role in the promotion of spermatozoa. The further the sperm moves in the female body, the less it comes into contact with the sperm plasma, which prepares it for a possible meeting with the egg [8]. It is known that spermatozoa are capacitated in portions for a period of 1-4 hours, due to which there is a constant change in the pool of gametes ready for fertilization of the egg [9; 12].

Cervical mucus throughout the ovarian-menstrual cycle can significantly complicate the sperm's progress into the uterine body itself. The fact is that the optimal composition of cervical mucus is formed only at the time of ovulation, mainly under the influence of ovarian estrogens. During this period, mucus mycelium forms peculiar spiral chains oriented along the lines of force of the earth's magnetic field. Having thus reached the body of the uterus, the remaining spermatozoa enter a favorable environment where they can maintain their viability for up to 3-4 days. In addition, the uterine environment has an activating effect on male germ cells, increasing their mobility [10]. Also, under the influence of progesterone, firstly, the content of sterols in the sperm plasma decreases, which leads to an increase in its permeability, secondly, the intracellular concentration of calcium ions, bicarbonate and superoxide radical increases, which leads to the activation of adenylate cyclase, as a result of which the cAMP content increases in the cell and cAMP-

dependent tyrosine phosphorylation occurs membrane and cytosolic proteins [11; 13]. Impaired sperm motility or its complete absence is one of the most important factors of male infertility.

In addition, in men with asthenozoospermia, there is a slowdown in the phosphorylation of tail proteins during capacitation. Phosphorylation in the cervix is important for the subsequent binding of the sperm to the shiny shell [9; 12; 16]. In reality, even pathological spermatozoa are able to fertilize an egg, but in this case it is impossible to say how functional the contribution of genetic and epigenetic material carried by such a sperm is [17].

After the above changes, the capacitated spermatozoa are ready for fertilization. Chemotaxis begins, that is, the recognition of the egg by secreted signaling molecules-gamones.

The result of capacitation is the ability of spermatozoa to acrosomal reaction, including complex ultrastructural and biochemical changes occurring on the surface of the sperm head: fusion of the plasmalemma with the outer acrosomal membrane, formation of hybrid membrane vesicles and loss of the acrosomal cap [4]. In the process of the acrosome reaction, the front part of the acrosome cover swells first. Then the fusion of the membranes leads to the subsequent dropping of the cover (vacuolization) and the release of the contents of the acrosome. As a result of the acrosome reaction, proteolytic enzymes such as hyaluronidase, acrosine and esterase are released. The above-mentioned enzymes, the flow of tubal secretions and the overactive mobility of capacitated spermatozoa facilitate the passage of cells through the radiant crown of the egg, and a large number of spermatozoa are needed to disperse and loosen the layer of follicular cells [14; 18].

Then the spermatozoa come into contact with the shiny zone, the receptors of their head interact with the ligands of the egg, the acrosome merges with the shiny shell and pours out its contents, dissolving it (Fig. 4) Fusion occurs under the condition of adequate interaction with the proteins of the shiny shell ZP3 and ZP4, the structure of which is species-specific, so that the acrosome reaction can develop only with the interaction of gametes representatives of the same species [19].

A tubercle of fertilization is formed outside – a section of the cytoplasm of the egg, to which only one sperm is attached. After that, the plasma membranes of the egg and sperm merge by forming a cytoplasmic bridge. The nucleus and centriole of the sperm penetrate into the cytoplasm of the oocyte, and the membrane of the sperm becomes one with the plasmalemma of the egg. The flagellum of the sperm detaches and resolves. A polyspermia block forms around the egg, preventing the penetration of other spermatozoa [1]. The polyspermia block is provided by the cortical reaction of the egg, which is accompanied by an increase in the level of calcium ions in the ooplasm and is manifested by a contraction of the cytoplasm, followed by the release of dense cortical granules into the periovular space, as well as an electrical reaction rapidly spreading through the oolemma and destroying zona pellucida ligands. At the same time, a critical factor for the implementation of these events is the oscillation of the concentration of calcium ions in the oocyte caused by the sperm.

The head of a sperm with a haploid nucleus turns into a male pronucleus, the female nucleus into a female one. The pronuclei merge, a diploid zygote is formed, which is fragmented mitotically. Thus, only one out of several million sperm cells carries out one of the most important processes on earth – fertilization. The remaining spermatozoa remain active after the acrosome reaction for only 2-3 hours; if they do not meet with the egg, they will lose their ability to fertilize and die [3; 22]. Thus, one part of the spermatozoa that enter the female body simply flow out of the vagina along with sperm, others die due to the high acidity of vaginal secretions, others die on the way to the fallopian tubes, they are absorbed by the mucous membrane of the uterus, where their phagocytosis occurs, and the fourth, the most active, which is important to consider in In forensic practice, they can generally reach the abdominal cavity, where they are also phagocytized and lysed within 20 hours. Dead spermatozoa decompose. One part of the decomposition products exits the vagina and is removed by washing [10; 23]. It can be concluded that the life expectancy of spermatozoa varies greatly: it all depends on the environment in which the sperm is located and the physiological factors that affect it. In the male body, spermatozoa form clusters in the

appendages of the testes until the moment of ejaculation, but if ejaculation does not occur, then they die here, then new male germ cells are formed. The full life cycle of spermatozoa is about 70-90 days, that is, the complete renewal of the cellular composition of spermatozoa occurs once every three months [7]. After exiting the male body in the air, spermatozoa almost immediately (within 15-20 minutes) die from bright light, high or low ambient temperature, but at room temperature and in the absence of direct sunlight they remain viable for 3-4 hours.

Fertilization is possible, for example, by mechanically depositing sperm from a napkin, hands or underwear onto the female genitals. On the surface of the body, as a rule, spermatozoa are also active for several hours and retain the ability to fertilize an egg for some time after drying (on average no more than half an hour). In the vagina, due to the predominance of an acidic environment, spermatozoa do not live long – 1-2 hours [24]. When moving into the cervix, their life expectancy increases to 3-5 days, depending on the phase of the ovarian-menstrual cycle, it happens that the sperm can stay in the fallopian tube for up to 8 days, but at the same time losing its ability to fertilize. Moreover, before the acrosomal reaction, the capacitated spermatozoa are capable of fertilization for 24 hours, and after its passage, the spermatozoa are active for only 2-3 hours. In the most favorable conditions, when spermatozoa are in the cervical mucus against the background of a high content of estrogens in the body, the fertilizing ability of spermatozoa persists up to 2 days after ejaculation [9; 11].

So, the life cycle of a sperm is quite complex, largely depending on the main purpose of the male germ cell. To date, the life cycle of the sperm has not been fully studied, as well as the processes occurring during its development, maturation, and participation in fertilization. It is obvious that the introduction of new functional markers, which could be an unambiguous way to assess the fertility of human spermatozoa, is extremely necessary. Undoubtedly, the sperm, like the egg, is the main link in ontogenesis, therefore, further study of its life cycle is necessary to level the problems of infertility and prenatal pathologies.

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