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UROGENITAL INFECTION AS A FACTOR OF DEVELOPMENT OF MALE INFERTILITY

To date, according to statistics, in Ukraine there is an increase in the number of infertile marriages. Many studies have emphasized the male factor of infertility. Often, male infertility is the result of a previous infectious disease or an acute genital inflammation. Microorganisms that infect sperm usually persist in the urinary tract as a monoinfection or form associations. Microorganisms in biofilms are able to acquire new, not yet studied, properties. Persistence of pathogens in the urogenital tract of men triggers several mechanisms of the pathological action on sperm, the first of which is the infectious factor, directly related to the adhesion and resulting in a complete or partial decrease in the mobility and deformation of sperm. On the other hand, the development of the inflammatory process as a trigger of an immune response directed simultaneously against the infectious agent and the affected sperm. The increase in the number of leukocytes at the site of inflammation activates the secretion of biological substances which also have a damaging effect on sperm. The generalized data allow drawing a conclusion about the significant influence of opportunistic and pathogenic microorganisms as part of associations or monoinfection on the morphofunctional state of spermatozoa.

Keywords: male infertility, spermatozoa, genital infections, microbial biofilms.

The structure of pathogens of infectious diseases has undergone significant evolution in recent years. Microorganisms that cause inflammatory diseases of the genitourinary system are of no exception. Against the background of intensive development of modern medical technologies, the number of patients with varying degrees of male fertility disorders is constantly increasing due to the direct or indirect action of various microor-

ganisms. Clinical experience has shown that in most cases latent and chronic forms of urogenital infections prevail, which greatly complicates the timely diagnosis. Such forms of infectious diseases are difficult to diagnose because their clinical symptoms are erased or absent. Therefore, patients rarely seek treatment. This, in turn, stimulates the selection of microorganisms with new sets of determinants of virulence, which ensure the adapta-

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tion of the pathogen to new conditions. The pathology progresses and is often complicated by the development of infertility [1, 2]. To date, there is a direct link between male infertility and bacterial infections of the genitourinary tract, which are associated with 6—10% of the cases of male infertility [3, 4]. There are several potentially open questions about the validity of a significant increase in cases of male infertility caused by individual representatives or associations of opportunistic pathogens. The etiological structure of inflammatory diseases of the genitourinary system is dynamic as the causative agents of these processes are characterized by various pathogenic factors.

It should be noted that microbial virulence factors and the degree of colonization play an important role in the development of the infectious process. In one case, this can cause inflammation of the genitourinary system, and in another — supports inflammation of the urogenital tract initiated by other factors. The inflammatory process is often accompanied by an increase in the number of immunocompetent cells, neutrophils, inflammatory mediators that produce free radicals and reactive oxygen species. There is a significant amount of research concerning the mechanisms and conditions of formation of stable states of uropathogenic bacteria and their key role in understanding the pathogenesis of urogenital infections. But there is very little research that concerns the ultrastructural organization and morphological variability of stable cellular forms of microorganisms, as well as their differentiation, which determines the heterogeneity of the population of urogenital pathogens.

In recent years, a number of reviews have been published on bacterial-induced apoptosis or programmed cell death. These comprehensive reports bring together many scientific studies conducted over the last decade in this area, starting with the first demonstrations of the fact that under certain conditions, enteropathogenic *Shigella*, and some viruses, including human immunodeficiency virus, cause the programmed

death of macrophages. Microorganisms directly manipulate the apoptotic mechanism in human cells to benefit their own survival and resilience. This explosion of new information about bacteria-induced apoptosis as well as the involvement of various molecular mechanisms by bacteria that cause PCD argues that apoptosis plays a key role in microbial pathogenesis and antibacterial immunity. In that connection, it should be noted that DNA damage to sperm and their apoptosis is considered a potentially useful indicator of male fertility. Sperm DNA integrity is important for accurate transmission of genetic information. Any form of sperm chromatin abnormality or DNA damage can lead to infertility in men.

In practice, all of the above causes of infertility are often underestimated, although they deserve considerable attention, since the frequency of urogenital diseases of microbial etiology remains quite high and does not tend to decrease.

Infectious factor in male infertility. Male infertility is a multifactorial syndrome that includes a wide range of disorders and various pathological conditions. To date, there have been dozen factors that can lead to male infertility. One of the most common causes is an infectious factor, which is closely related to acute and chronic diseases of the genitourinary system, adverse environmental effects, endocrine and immunological disorders, and genetic disorders. As a rule, inflammatory processes in the genitals of men occur with minimal symptoms or asymptomatic, therefore the analysis of results of their bacteriological research acquires a special value. With its help, it is possible to give a semi-quantitative assessment of the general microbial pollution, determine the condition of the epithelium, detect inflammation and determine the composition of the microflora, and to detect the presence of pathogenic factors of microorganisms.

The male genitals, where the bacterial flora is localized, include the urethra, prostate, testicles, and their appendages. The composition of the urethra microbiota in men remains largely un-

changed throughout life. Already at birth, *Staphylococcus epidermidis* is found in the urethra of boys, which is a natural inhabitant of healthy person's microbiota. In the outer part of the urethra and genitals, there are *Mycobacterium smegmatis*, which are morphologically similar to *Mycobacterium tuberculosis* and *Staphylococcus epidermidis*, *Streptococcus*, as well as *Peptococcus*, *Peptostreptococcus*, *Enterococcus*, in particular, *Enterococcus faecalis*. *Campylobacter ureolyticus*, formerly known as *Bacteroides ureolyticus*, is present in the human amniotic fluid and genitourinary tract [5, 6]. In most cases, microorganisms damage the tissues of the reproductive organs, destroy the hematotesticular barrier, which separates blood from germ cells participates in the regulation of spermatogenesis, and provides isolation of antigenic cells of spermatogenic epithelium from the body's immune system. Damage to this barrier is an important factor in the occurrence of disorders of spermatogenesis (oligo-, terato-, and azoospermia) [7]. On the other hand, it creates a microenvironment for the formation of the liquid part of sperm.

Chlamydia trachomatis, *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, *Trichomonas vaginalis*, and *Mycoplasma hominis* are the most common pathogens of bacterial urethritis. According to some authors, also quite often, causative agents of urogenital infections are *Escherichia coli*, found in about 80% of cases, and *Staphylococcus saprophyticus*, which causes inflammation in the genitourinary tract in 15% of cases [8, 9]. Bacterial urethritis, as the main disease, can be accompanied by various urogenital bacterial infections, which include prostatitis, epididymitis, orchepididymitis, proctitis, or reactive arthritis. It is considered that the causative agents of chronic bacterial prostatitis are often gram-negative pathogens such as various strains of *Escherichia coli*, as well as *Klebsiella*, *Serratia*, *Proteus mirabilis*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* [10–14]. Cases of chronic

bacterial prostatitis caused by *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis*, *Salmonella* spp., *Clostridia* spp., Anaerobes, and parasitic and fungal microorganisms have also been described [15]. Chronic bacterial prostatitis increases the risk of developing antisperm antibodies in sperm plasma [16]. In another meta-analysis, a clear correlation was also found between chronic prostatitis and the level of antisperm antibodies. These data suggest that chronic prostatitis adversely affects the reproductive function of men [17, 18].

The violation of the integrity of the mucosa of any genesis in the affected area develops an inflammatory reaction, introduction of microorganisms, and development of a pathological process. Due to the pathological effects of bacteria on men, there is a decrease in the volume and changes in the chemical and biochemical composition of sperm, increase in its viscosity and dilution time (viscosopathy), and pH deviation. Sperm motility is reduced (akinozoospermia), and its morphology is disturbed (teratozoospermia); antisperm antibodies of the IgG and IgA classes are produced. In addition, the number of peroxidase-positive leukocytes (purulent cells), which produce reactive oxygen species and a large number of cytokines, increases. They adversely affect the functional state of sperm, disrupting its ability to fertilize, and cause apoptosis of sperm.

Bacterial monoinfection as a risk factor for male infertility. Bacteria that cause acute and chronic inflammatory processes in the urethra as a monoinfection occur in 10–35% of cases. Each of these pathogens directly or indirectly affects the development of different types of pathospermia. Many bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, protozoa, viruses and fungi, are able to attach to the sperm membrane and directly affect it [19, 20].

The dominant place among the infections of the genitourinary system of men is taken by protozoa, in particular *Trichomonas vaginalis*, although trichomoniasis is usually asymptomatic. However, *Trichomonas* affects the urethra, semi-

nal vesicles, and prostate. Urogenital trichomoniasis causes complications such as balanitis, balanoposthitis, urethritis, paraurethritis, cuperitis, epididymitis, prostatitis, vesiculitis, and cystitis. *Trichomonas* infections are controversially discussed in terms of their effects on sperm because there is little information on the effects of pathogenic factors of *T. vaginalis* on sperm. *T. vaginalis* significantly reduced motility, viability, and functional integrity of sperm depending on the concentration and time *in vitro*. In addition, several researchers have noted abnormalities in sperm parameters infected with *T. vaginalis*, such as decreased sperm motility and viability and decreased percentage of sperm cells with normal morphology [21–23]. Although according to FR Oxendorf and Soper, *Trichomonas vaginalis* is more common in infertile men than in control groups, no effect on the motility and interaction of sperm and mucus can be demonstrated [24].

Mycoplasma hominis is responsible for one of the most common sexually transmitted infections. Widespread urogenital mycoplasmas and their frequent detection in almost healthy people make it difficult to determine the role of these microorganisms in the pathogenesis of urogenital diseases. Although, according to some researchers, *Mycoplasma hominis* is an opportunistic pathogen, justifying this by the possibility of isolating it from clinically healthy individuals, as well as asymptomatic clinical course of urogenital mycoplasmosis [25]. However, it should be noted that a lot of work has been done to study the effect of *Mycoplasma hominis* on sperm morphology and motility [26], the ability to respond to acrosomal reactions, and the effect on sperm nuclear integrity [27]. Moreover, microorganisms increase in size as the infection progresses, as well as attached mycoplasmas undergo morphological changes from bulb-like shape to spherical shapes. According to F.J. Diaz-Garcia and A.P. Herrera-Mendoza (2006), the maximum interaction of *M. hominis* (at an infectious dose of 480 cells) with sperm was observed 10 min after infection and

is probably accompanied by the loss of sperm receptor function due to excessive secretion of toxic pathogenic factors of mycoplasma.

Escherichia coli is most common among urogenital infections [28–30] as a monoinfection that can damage sperm in various ways. Bacteria were isolated from semen in 69% of the patients with prostate pathology [31]. Moreover, *Escherichia coli* causes a variety of inflammatory diseases of the urogenital tract, such as urethritis, epididymitis, and orchitis. Due to the direct action of its adhesion factors, in particular fimbriae type 1 *Escherichia coli* attaches to specific receptors (α -galp-1,4- β -galp-O-methyl, mannose) of sperm and causes its agglutination [32, 33, 34]. The bacterium causes damage mainly to the plasma membrane of sperm [35], blistering and rupturing the inner and outer membranes of the acrosome, reduces sperm motility [36], and affects the viability and potential of mitochondrial membranes through direct contact or mediated by soluble metabolites. The pathogen indirectly induces the formation of autoantibodies to sperm. *Escherichia coli* infection causes sperm apoptosis [37–39] regardless of the reactive oxygen species, due to the presence of lipopolysaccharides and purines. It should be noted that all gram-negative bacteria have a similar effect on sperm [40].

Enterococcus faecalis is present in the normal intestinal flora, but it is also found in the male urogenital tract. *Enterococcus spp* is one of the most common pathogens of epididymitis that mainly reach and colonize the epididymis by retrograde rising through the urethra [41, 42]. Moreover, *Enterococcus faecalis* has been repeatedly detected in sperm cultures of infertile men associated with significantly poorer sperm quality as well as changes in sperm plasma composition, crucial for sperm survival [43, 44]. Mehta and E. Moretti (2009) reported that *Enterococcus faecalis* was present in about 53% of the semen samples of male partners in infertile couples and was associated with a high incidence of oligozoospermia and teratozoospermia [45, 46]. The

most studied factors of pathogenicity of *Enterococcus faecalis* are aggregation substance, surface adhesives, in particular the surface protein Esp, which provides colonization and stability of *E. faecalis* in the urinary tract [47]. Although no significant depressant effect of enterococci on sperm motility was observed, some researchers described a negative effect on the integrity of the membrane of the head, neck, and body of human sperm [48], probably mediated by hemolysin, a known enterococcal virulence factor.

Many experimental *in vitro* studies have been devoted to the relationship between chlamydial infection and sperm quality. According to Cengiz T, Al-Mously N, and Cross N.A., *C. trachomatis* infection is associated with poor sperm quality [49, 50]. Others argue that this is not the case [51, 52]. The prolonged infectious process caused by chlamydia is asymptomatic in 85–90% of infected people [53] and leads to the formation of pathospermia in 20% of patients. Some reports indicate that *C. trachomatis* infection is associated with decreased sperm concentration and motility, as well as changes in sperm pH and decreased ejaculate volume [54–58]. In addition, the mi-

croorganism disrupts the acrosomal response of sperm [59, 60]. Conversely, the other studies have found no link between the male genital tract infection with *C. trachomatis* and the changes in sperm quality [61–66]. Antibodies to chlamydial infection are found in 15.4% of infertile men, even in the absence of signs of inflammation of the genitourinary tract [67]. Thus, the available evidence is contradictory and still makes it impossible to establish a clear link between *C. trachomatis* infection and sperm quality [68–71].

It should be noted that chlamydial infection, damaging sperm, which is often accompanied by agglutination and the appearance of anti-sperm antibodies, not only worsens the basic parameters of the spermogram but also increases DNA fragmentation. *In vitro* studies to establish a relationship between the markers of apoptosis in sperm and chlamydial infection have shown that *C. trachomatis* interacts with sperm cells, affecting their function and inducing apoptosis [72–74]. Gallegos et al. (2008) reported that in patients with *C. trachomatis* in the genitourinary system, sperm DNA fragmentation increases compared to controls (Table 1).

Table 1. Data analysis on the impact of infectious factors on sperm parameters

Causative agent of disease	Morphological changes	Functional changes	Apoptosis DNA fragmentation Phosphatidylserine translocation	Amount of sperm Acrosomal reaction	Reference
<i>Escherichia coli</i>	+	reduces sperm motility	+ ? +	+ reducing the amount of sperm + change	Sanocka-Maciejewska D., 2005; Köhn FM, 1998; El-Mulla KF, 1996.
<i>Staphylococcus haemolyticus</i>	+	+	+ + +	+ reducing the amount of sperm	Ghaed'a J, 2018; Vilvanathan V, 2016
<i>Campylobacter ureolyticus</i>			+ + +		Bullman S, 2013
<i>Chlamydia trachomatis</i>		reduces sperm motility	+ ? ?		Satta A, 2006

Causative agent of disease	Morphological changes	Functional changes	Apoptosis DNA fragmentation Phosphatidylserine translocation	Amount of sperm Acrosomal reaction	Reference
<i>Mycoplasma hominis</i>	+ bent tails of sperm	+	+ + ?		Gallegos G, 2008 Rose BI, Scott BS., 1994
<i>Ureaplasma urealyticum</i>	+ twisting the tail of sperm, agglutination of sperm, increase in abnormal shape of sperm	+	+ + +		Sellami H, 2014; Xue-Jun Shang I, 1999
<i>Ureaplasma parvum</i>	+	+	+ + ?		Gdoura R., 2007
<i>Mycoplasma genitalium</i>			+ + ?	+ reducing the amount of sperm	Gdoura R., 2008
<i>Neisseria gonorrhoeae</i>		+			Harvey HA, 2000.
<i>Pseudomonas aeruginosa</i>		+			Huwe P, 1998
<i>Staphylococcus aureus</i>	+	+			Isaiah I., 2011; Merino G, 1995
<i>Staphylococcus saprophyticus</i>	+	+			Isaiah IN, 2011
<i>Gardnerella vaginalis</i>	+	+		+ reducing the amount of sperm	De Francesco MA, 2011.
<i>Trichomonas vaginalis</i>	+	+		+ reduces the viscosity of semen	Roh J, 2015; Skerk V et al, 2002
<i>Corynebacterium glucuronolyticum</i>		+ reduces sperm motility, changing pH of semen			Meštrović T, 2018.
<i>Enterococcus faecalis</i>	+	+		+ reduces the viscosity of semen	Qiang H, 2007; Moretti E, 2009
<i>Klebsiella pneumoniae</i>	+	+			Zuleta-González MC, 2019
<i>Proteus sp.</i>		+			Enwuru CA, 2016
<i>Morganella morganii</i>		+	+		Josep U, Marcos A, 2013

Asymptomatic transmission of *Ureaplasma urealyticum* is common to most people, and there is an insufficient evidence of the need to detect and treat this infection, so routine detection and treatment of asymptomatic or symptomatic men and women have not been recommended [75–77]. The questions whether microorganisms affect sperm parameters and whether examinations and treatments are needed are controversial. On the other hand, some studies suggest that the presence of *U. urealyticum* and *Mycoplasma hominis* is associated with abnormal sperm parameters [78] and sperm viability. In addition, the progressive motility of the sperm of *U. urealyticum*-infected men was significantly lower than for uninfected men [79, 80], the average sperm concentration was also lower [81]. According to the literature, *U. urealyticum* violates the integrity of the sperm membrane, reduces motility, and changes in the structure of chromatin. The relationship between *U. urealyticum* infection and sperm quality or fertility is also discussed. *U. urealyticum* may attach to the sperm membrane and initiate some enzymatic reactions that may adversely affect the sperm membrane and lead to a decrease in the assessment of hypoosmotic edema. *U. urealyticum* attached to sperm produces metabolites such as superoxide and hydrogen peroxide, which can adversely affect the integrity of the sperm acrosome by breaking down the lipids of the acrosomal membrane.

Neisseria gonorrhoeae is an exclusive human pathogen that mainly affects the urogenital epithelium. In chronic urethritis caused by *Neisseria gonorrhoeae*, the formation of strictures of the urethra and the development of its obstruction and ejaculation disorders are possible [82–84]. Gonococci are able to attach to sperm cells through the villi of the bacterial cell surface [85–87], thereby causing changes in sperm motility.

According to our data, infectious factors play a significant role in the development of various forms of azoospermia.

So, the number of men with a history of Trichomonas infection in non-obstructive azoospermia (NOA) was 1.6%, and in obstructive azoospermia (OA) — 1.5% (Table 2).

The frequency of detection of chlamydia by PCR in NOA was 3.3%, and in OA — 2.9%. Mycoplasma in NOA was detected in 5.7% of men tested, and in OA — in 2.9%. Ureaplasma was diagnosed in 12.3% in NOA and in 11.7% in OA. In NOA, gonorrhoea was detected in 6.6%, and in OA — in 13.2%. Herpes simplex virus type 2 was observed in 5.7% of men with NOA and in 7.3% of men with OA. Gardnerella was diagnosed in 9.0% of men with NOA and 13.3% of men with OA.

In accordance with the results for bacteriological culture, the species spectrum of opportunistic pathogens in the ejaculate or prostate secretion of men with azoospermia in diagnostically significant titers was various, but with low indicators (Table 3).

The frequency of enterococci in men with azoospermia in OA was 32.3%, almost twice higher than in PLA (17.2%). Infection of ejaculate/prostate secretion with *Escherichia coli* in NOA was detected in 13.1% of patients, and in OA — in

Table 2. Sexually transmitted infections in men with azoospermia

Transferred infections of men with azoospermia	Non-obstructive azoospermia, number (%) (N = 122)	Obstructive azoospermia, number (%) (N = 68)
<i>Ureaplasma urealyticum</i>	15 (12.3%)	8 (11.7%)
<i>Trichomonas vaginalis</i>	2 (1.6%)	1 (1.5%)
<i>Chlamidia trachomatis</i>	4 (3.3%)	2 (2.9%)
<i>Micoplasma genitalium</i>	7 (5.7%)	2 (2.9%)
<i>Neisseria gonorrhoeae</i>	8 (6.6%)	9 (13.2%)
Herpes simplex virus 2-type	7 (5.7%)	5 (7.3%)
<i>Gardnerella vaginalis</i>	11 (9.0%)	9 (13.3%)
Total	52 (44.2%)	36 (52.8%)

23.5%. *Staphylococcus aureus* was detected only in patients with OA (4.4%). β -hemolytic streptococcus was detected in both NOA (7.4%) and OA (13.2%). *Epidermal streptococcus* is found in men in OA only — 4.4%.

Noteworthy, correspondence of bacteriospermia to the data of clinical examination of men with a history of chronic inflammatory diseases of the genital organs is evident. By the data in Table 2, microbial contamination of ejaculate and prostate secretion samples was predominant in men with OA (77.8%) compared to 37.7% in men with NOA. It should be noted that the question of the role of subclinically and clinically pronounced infections of the male genital tract in the formation of infertility is still being debated. Different mechanisms are involved in the disruption of the process of spermatogenesis and sperm quality caused by infection of the gonads or inflammatory processes of the urogenital tract. Leukocytes are markers of infection, but there are controversial views on their effects on seminal plasma and male fertility. According to the WHO recommendations, 1 million leukocytes in 1 mL of ejaculate should be considered as the limit of leukocytospermia. However, many studies have not found a correlation between the number of leukocytes and the number of sperm progenitor cells or their functions [88].

Table 3. Bacteriological examination of ejaculate/prostate secretion

Infectious factors	Non-obstructive azoospermia, number (%) (N = 122)	Obstructive azoospermia, number (%) (N = 68)
<i>Enterococcus faecalis</i>	21 (17.2%)	22 (32.3%)
<i>E. coli</i>	16 (13.1%)	16 (23.5%)
<i>Staphylococcus aureus</i>	—	3 (4.4%)
β -hemolytic streptococcus	9 (7.4%)	9 (13.2%)
<i>Epidermal streptococcus</i>	—	3 (4.4%)
Total	46 (37.7%)	53 (77.8%)

The most common method of identifying a bacterial infection of the male urogenital tract is microbiological culture of seminal fluid or prostate juice. If after classical sowing, the number of colonies of pathogens is large, there is a version of the probable damage to the spermatogenic epithelium or sperm by free oxygen radicals. They are always in excess contained in infected biological fluids because in the inflammatory process they migrate phagocytes with activated oxygen-dependent enzymes. However, the question whether the detected infectious factors always cause azoospermia is not straightforward [89]. It cannot be ruled out that it is only a combination of asymptomatic infection with another (underlying) pathology.

It should be noted that the infection caused by *Ureaplasma urealyticum* is the most dangerous for male reproductive function [90]. Our studies have revealed the highest percentage of this pathogen among the other microorganisms: in men with NOA — 12.3%, and with OA — 11.7%. This is the most common microorganism that infects the male reproductive system. It changes various characteristics of the process of spermatogenesis, as well as spermatogenic epithelium and sperm. Also, it affects the concentration of cytokines such as IL-6, IL-8, TNF- α , and INF- γ .

So, the results obtained indicate that infection of the male urogenital tract and infection of seminal fluid or prostate juice are important factors causing the development of NOA and OA.

Microbial biofilms as a risk factor for male infertility. According to most authors, sexually transmitted infections as mono-infections are rare, but in the form of biofilms, they cause a mixed acute or chronic bacterial process that determines the topography and severity of the lesion [91—93]. Approximately 65% of all chronic human infectious diseases are associated with biofilms [94, 95]. It is believed that enterobacteria and staphylococci are the main causative agents of bacterial urethritis among the opportunistic pathogens that have the greatest tendency

to form bacterial biofilms [96, 97]. Although, according to the analysis of literature data, *Escherichia coli*, *Staphylococcus haemolyticus*, *Campylobacter ureolyticus*, *C. trachomatis*, *Candida albicans*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma genitalium*, *N. gonorrhoeae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus viridans*, *Staphylococcus saprophyticus*, *Gardnerella vaginalis*, *Trichomonas vaginalis*, *Corynebacterium glucuronolyticum*, *Trichomonas vaginalis*, *E. faecalis*, *K. pneumoniae*, and *Proteus* can form biofilms, especially under the influence of stressors. There is ample evidence that bacteria that move due to flagella and contain other microbial determinants of virulence, such as fimbriae and pilli, which contain specific adhesive proteins such as intimin, YadA, Inv, and Ail, have a special activity in creating a biofilm [98—101]. The development of the biofilm can be considered as a determinant of virulence, which is responsible for the long-term resistance of bacteria in the genitourinary tract [102].

A unique property of polymicrobial biofilms is a set of protective mechanisms that bacteria of different species acquire as a result of the exchange of genetic materials, such as plasmids, genetic cassettes, transposons, and bacteriophages. It is especially important for practical medicine that bacteria in biofilms have a high level of resistance to stressors, immune protection factors, and antibiotics [102, 104]. The basis of increased stability is the properties of cells of microorganisms and the extracellular matrix, which are associated with a decrease in their free surface due to contact with each other. Tolerance of microbial biofilm is an indirect ability of microorganisms to resist the action of antibiotics by slowing down metabolism and «switching off» the main biological processes of the cell [105, 106], as well as the formation of persistent bacterial cells, also called VBNC-forms (viable but non-culturable). It is in the middle layers of the biofilm that persistent bacteria are concentrated [107, 108], the

most common of which are *Escherichia coli*, *S. aureus*, *E. faecalis* [109—111], *M. tuberculosis*, *C. trachomatis* [112], and *P. aeruginosa*. Persistent bacteria and VBNC are associated with chronic infections and are both present in bacterial biofilms [113—116] and have the ability to recover when returned to favorable conditions [117, 118]. The ability of microorganisms to adapt to harsh environmental conditions can be an advantage over other species.

The ability to form biofilms has been registered not only in strains of pathogenic and opportunistic microflora but also in microorganisms that do not have a cell wall, namely mycoplasmas [119, 120]. It is known that genital mycoplasmas, in particular *M. genitalium* and *M. hominis* as well as *U. parvum* and *U. urealyticum*, colonize the male reproductive system. As ureaplasmas and mycoplasmas can colonize the male reproductive tract, their participation in male infertility can be suspected, but the results of studies by various authors remain contradictory. In particular, it has not been possible to demonstrate the relationship between altered sperm parameters in infertile men and the presence of these bacteria in semen [121]. However, a meta-analysis comparing the results between infertile men and controls showed an association with the risk of infertility in the presence of *M. hominis* and *U. urealyticum*, *M. genitalium*, and *U. parvum* [122]. Such results indicate that in the presence of the associations or in the formation of biofilms, the percentage of development of the infectious process and the development of different types of pathospermia increases. This conclusion can be traced in the clinical course of urogenital chlamydial infection where the high frequency of associations of chlamydial infection with other bacterial and viral infections correlates with the increased risk of chronic inflammatory processes of the male urogenital tract and predisposition to reinfection.

In the case of both monoinfection and biofilm formation, the main stage of development

of pathological process is intercellular interaction. There is insufficient information in the literature on intercellular contacts of microorganisms, which reflect the patterns of development of microbial populations, and their impact on the development of pathological processes, especially in the urogenital tract. One of the modern directions of microbiology is the study of the adhesive properties of microorganisms. Representatives of the normal microflora along with pathogenic microorganisms and various types of immunoglobulins and immunocompetent cells have adhesive properties. As for the adhesion of bacteria in the context of different types pathospermia, there are two separate mechanisms. The first is based on the development of a pathological process associated with direct or indirect pathological action of the pathogen on sperm. In particular, the adhesion of pathogenic and conditionally pathogenic microflora on the membranes of host cells and their penetration inside the cell is the first stage of interaction and the trigger for colonization. Microorganisms stick to the sperm membrane, gradually penetrating into the cell, turn off its most important defense mechanism, which prevents the fusion of lysosomes with phagocytic vacuoles, in particular, blocks the Raba protein system. This is one of the mechanisms that allows bacteria to carry out intracellular parasitism. We can assume that in microbial associations, the number and duration of interaction of bacteria with sperm, as well as the stability of their contacts increase. As a result, various pathological processes occur, such as the adhesion of microorganisms to sperm and the adhesion of sperm cells to each other (agglutination) and the attachment of sperm to other cells (aggregation). This leads to the development of various types of pathospermia, such as akinozoospermia (complete immobilization of sperm), necrosospermia (absence of live sperm in the ejaculate) or asthenozoospermia (reduction in the number of motile sperm). Another mechanism is related to the influence of adverse

factors, including the use of antibiotics, hormone therapy, radiation, the development of immunodeficiency, as well as mental stress, which cause dysbiosis. This increases the number of opportunistic pathogens. Its growth is accompanied by a change in pH from 3.8—4.4 to 6.8—8.5. As a result, favorable conditions are created for the colonization of the genital tract by ureaplasmas and mycoplasmas.

Immune system cells as a risk factor for male infertility. Sperm have a set of chromosomes other than somatic cells, and are thus perceived as foreign cells to their own body. Therefore, the activation of the pathological effect of the immune system on sperm is primarily due to the adhesion of immunoglobulins. The hematotesticular barrier performs a protective function for sperm that has undergone crossover. When the integrity of the hematotesticular barrier is violated due to injuries, surgical manipulations, or infectious diseases, immunoglobulins G, A, and M, as antisperm antibodies, bind to various antigens on the sperm surface [123—126]. To date, the best studied sperm antigens are as follows: PH-20 (sperm head antigen), SP-10 (sperm protein antigen), HAS-63 (human sperm antigen), fertilization antigen (FA-1 1), FA-2 (antigen fertilization 2), CS-1 (signal-dividing antigen), and SAGA-1 (spermagglutination antigen 1) [127, 128]. This type of interaction is characterized by agglutination and fixation of sperm, which induces the formation of immune complexes. According to Vikram AS, Kuldeep Dhama et al., the presence of ASA in semen significantly reduces the concentration and motility of sperm [129—134]. In addition, the authors have found that antisperm antibodies affect sperm's morphology, viability, volume, and motility.

According to the analyzed data, it can be stated that antibodies present in seminal plasma affect the immobilization and agglutination of sperm. Antibodies attached to the sperm head can inhibit the acrosomal response and can cause damage to the genetic material inside the

sperm. When an antibody is fixed on the sperm surface, the complement is activated according to the classical variant with the formation of a membrane-attacking complex and subsequent lysis of the affected cell. In addition, C3 and C4 are present in semen, participate in the pathogenesis of antisperm antibodies [135], and can affect the self-agglutination of sperm with the formation of pathological processes such as oligospermia and azoospermia.

According to the literature, about 60% of the cases of male infertility are related to male genital infections. Pellati et al., Sandoval, and Raburn believe that this can cause an abnormal increase in the number of leukocytes in the ejaculate [136—138]. Elevated levels of white blood cells in semen (a condition called leukocytospermia) are defined by the WHO as the presence of over 1×10^6 white blood cells/mL in ejaculate (WHO, 2010), which can adversely affect sperm function, causing acrosomal lesions, defects of the middle part and tail [139, 140]. In addition, leukocytes are the main producers of reactive oxygen, which is harmful to the DNA of sperm and their membranes, so elevated white blood cell counts may negatively affect sperm quality. Proinflammatory cytokines produced by leukocytes also have a detrimental effect on sperm [141, 142], which in turn causes lipid peroxidation and subsequent formation of ROS by leukocytes. This leads not only to the deterioration in the quantitative indicators of sperm but also to the decrease in the ability of sperm to fertilize and to its genetic inferiority. Bacterial support for chronic inflammation of the urogenital tract is often accompanied by an increase in the number of neutrophils that produce free radicals and reactive oxygen species.

The microbiota causes the development of sperm apoptosis. During the inflammatory processes in the male genital tract, there is an increase in the amount of sperm that undergo apoptosis, which may be associated with the elevated levels of reactive oxygen species. However, another

factor that stimulates apoptosis may be the direct contact with bacteria or their products, even in the absence of ROS. Male semen, as a mixture of sperm and gonadal secretions that contains nutrients such as lipids, proteins, glycans, and inorganic ions, is an ideal environment for microbial growth. So no wonder that in numerous studies of materials from the genitourinary system of men, the most common are the following: *E. coli*, *Enterococcus faecalis*, *C. trachomatis*, *U. urealyticum*, *Staphylococcus haemolyticus*, *Mycoplasma genitalium*, *N. gonorrhoeae*, *Bacteroides ureolyticus*, *Pseudomonas*, *Lactobacilli*, *Prevotella*, *Finegoldia*, *Campylobacter*, *Actinomyces*, *Fusobacterium*, *Dialister*, *Peptoniphilus lactobacillus*, *Gardnerella*, and *Ureaplasma*.

We have already mentioned above the effect of individual microorganisms and bacterial communities on sperm, which leads to both morphological and functional changes in sperm counts. However, there are numerous opinions that gram-positive and gram-negative microorganisms are able to induce apoptosis of eukaryotic host cells [143—145], including sperm [146, 148, 149]. Mature sperm has been reported to contain clear markers of cell damage associated with apoptosis [150, 152, 153]. Stimulation of apoptosis may be due to the direct contact of sperm with bacteria or their products. The results of Villegas J.S. show that bacteria increase the externalization of the plasma membrane of sperm in ejaculated human semen. This method of inducing apoptosis does not require external ROS and may be the result of any of the molecular mechanisms that take into account changes in motility, vitality, and DNA integrity, which are characteristics of sperm in male genital tract infection [29]. Sperm DNA damage is partly related to male infertility [154, 155].

A eukaryotic cell enters the path of apoptosis if the following changes in DNA occur: the proapoptotic protein p53 is activated or the concentration of antiapoptotic protein hsp 70 is reduced [156, 157]. In addition, the apoptotic

marker is phosphatidylserine, which appears in the outer monolayer of plasma membrane lipids. In any of these cases, one of the mechanisms of apoptosis is realized, the main of which is: suicide signal → mitoptosis → apoptosis. Apoptotic markers, including mitochondrial transmembrane potential, phosphatidylserine externalization and DNA fragmentation, were detected simultaneously in ejaculated human semen after incubation with the known pathogen *Escherichia coli*, as well as with opportunistic strains of *Staphylococcus haemolyticus* and *Bacteroides ureolyticus*. Some experiments using a conventional TUNEL analysis have shown an increase in DNA fragmentation of human semen due to incubation with *C. trachomatis* and *Candida albicans* [158, 159]. It should be noted that the loss of asymmetry of phospholipids is one of the mechanisms by which bacteria interfere with ejaculated sperm with subsequent induction of their death pathways.

Quite a few authors are inclined to believe that direct contact of opportunistic bacteria and their toxins with ejaculated human sperm may play a role in promoting apoptosis, even to a greater extent than the known pathogenic strains of bacteria.

Conclusions. The above data allow us to conclude about the significant influence of opportunistic and pathogenic microorganisms, as part of associations or as individual microorganisms, on the morphofunctional state of sperm. A detailed study of the dynamics of biofilm formation in the genitourinary tract and the biological properties and patterns of functioning of microorganisms that are part of it, addresses a number of issues related to the development of infertility. Basing on the analysis of literature data as well as personal experience, the authors have determined the presence of morphofunctional changes in stable cellular forms of bacteria and their importance in adaptation strategies.

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УРОГЕНІТАЛЬНІ ІНФЕКЦІЇ ЯК ФАКТОР РОЗВИТКУ НЕПЛІДНОСТІ ЧОЛОВІКІВ

На сьогоднішній день за статистикою в Україні спостерігається зростання кількості неплодних шлюбів. У багатьох дослідженнях підкреслюється чоловічий фактор неплодності, який сягає 50 %. Часто чоловіча неплодність є наслідком перенесеного інфекційного захворювання або гострого запалення статевих органів. Мікроорганізми, що інфікують сперму, зазвичай локалізуються в сечовивідних шляхах як моноінфекція або утворюють асоціації. Мікроорганізми в біоплівках здатні набувати нових, ще не вивчених властивостей. **Метою** даної роботи було охарактеризувати інфекційні чинники, що спричиняють неплодність чоловіків із врахуванням моноінфекцій, мікробних біоплівок та імунної системи. **Методи.** Аналіз літературних і власних даних щодо впливу на неплодність чоловіків моноінфекцій уrogenітального тракту, мікробних біоплівок, клітин імунної системи та апоптозу, а також інфекційний скринінг виділень уретри, бактеріологічне дослідження сперми та секрету передміхурової залози, оцінка видового та кількісного складу мікрофлори уrogenітального тракту чоловіка. ПЛР-діагностику інфекцій, що передаються статевим шляхом, та інвазій проводили з використанням набору реактивів «ДНК-технологія» на автоматичному флуоресцентному аналізаторі. **Результати.** Стійкість збудників у сечостатевих шляхах чоловіків запускає кілька механізмів патологічної дії на сперму. Перший із них безпосередньо пов'язаний із прилипанням інфекційного чинника і призводить до повного або часткового зниження рухливості сперматозоїдів, а також їх деформації. *Mycoplasma hominis* відповідальна за одну з найбільш поширених інфекцій, що передаються статевим шляхом. При цьому мікроорганізми збільшуються в розмірі в міру протікання інфекції, і прикріплені мікоплазми також зазнають морфологічних змін. Хламідійна інфекція, пошкоджуючи сперму, часто супроводжується аглютинацією та появою антиспермальних антитіл, що не тільки погіршує основні показники спермограми, а й збільшує фрагментацію ДНК. *Ureaplasma urealyticum* порушує цілісність мембрани сперматозоїдів, зменшує їхню рухливість і змінює структуру хроматину. У роботі також розглядається взаємозв'язок між інфекцією *Ureaplasma urealyticum*, якістю сперми та неплодністю чоловіків. Уреаплазма може прикріплюватися до мембрани сперматозоїдів та ініціювати деякі ензиматичні реакції, які можуть негативно впливати на мембрану. Ентеробактерії та стафілококи є основними збудниками бактеріального уретриту серед умовно-патогенних мікроорганізмів, які мають найбільшу схильність до утворення бактеріальних біоплівок. Для практичної медицини особливо важливо, що бактерії в біоплівках мають високий рівень стійкості до факторів імунного захисту та антибіотиків. З іншого боку, розвиток запального процесу запускає імунну відповідь, спрямовану одночасно проти збудника інфекції та ураженої сперми. Збільшення кількості лейкоцитів у вогнищі запалення активує секрецію біологічних речовин, зокрема прозапальних цитокінів, які також пошкоджують сперму, зокрема сперматозоїди. Активація патологічного впливу імунної системи на сперму зумовлена насамперед адгезією імуноглобулінів. Імуноглобуліни G, A та M, як антиспермальні антитіла, зв'язуються з різними антигенами на поверхні сперматозоїдів, що значно знижує їхню концентрацію та рухливість. **Висновок.** Узагальнені дані дозволяють зробити висновок про значний вплив умовно-патогенних і патогенних мікроорганізмів у складі асоціацій або як моноінфекцій, що інфікують сечостатеву систему, на морфофункціональний стан сперматозоїдів і, як наслідок, на плідність чоловіків.

Ключові слова: неплодність чоловіків, сперматозоїди, уrogenітальні інфекції, мікробні біоплівки, імунна система.