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ROLE OF MICROBIAL FACTOR IN MALE INFERTILITY PATHOGENESIS. LITERATURE REVIEW

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ABSTRACT

The role of infectious pathology in the genesis of infertility is still being studied. The present review considers possible mechanisms of infertility development associated with the microbial profile of the male reproductive system. It makes an attempt to study the role of pathogenic properties of microorganisms in the development of infertile conditions if an inflammatory process is localized in the male urogenital tract, in particular its effects on the fertility properties of spermatozoa (reduction in their number, inhibition of their motility, changes in their morphology and fertilizing capacity).

Besides, the review presents a discussion on the role of reactivity and resistance of an organism in maintaining chronic inflammation in male reproductive organs.

Keywords: male infertility, microbial persistence, fertility

INTRODUCTION

There are many aspects in the medical component of infertility: male and female infertility, primary and secondary one, including infections of organs of the genitourinary system. At the same time, the role of infectious pathology in the genesis of infertility is still being studied. Some scientists believe that an increasing role of sexually transmitted infections is predominant, while others, on the contrary, emphasize that urogenital infections do not play a major role in the development of infertility [1,2,3]. A number of researchers show a preference for opportunistic microorganisms in this issue; others believe it is all the fault of pathogenic associations [4,5]. It is obvious that success can be achieved only with a fundamental solution of the problem through the lens of microbiology, biochemistry, general pathology, and pathological physiology, which have a methodological basis for it. Moreover, it is particularly important to compare the role of infection in fertile and infertile patients.

MICROBIAL ASPECTS IN MALE INFERTILITY PATHOGENESIS

It is seen from the analysis of literature [7,8,9,10,11,12,13] that the species composition of microorganisms vegetating in the semen of healthy men is dominated by gram-positive microorganisms represented by genera *Corynebacterium*, *Lactobacillus*, *Streptococcus* and *Staphylococcus* (coagulase-negative species). The dominance of these groups of microorganisms in the semen of healthy men may be related to the peculiarities of seminal plasma: the presence of lysozyme, complement, secretory immunoglobulins, defensins, with their bactericidal action directed primarily against gram-negative microorganisms [14,15,16,17,18,19,20]. At the same time, the semen of infertile men shows a deficiency of coryneformic bacteria and lactobacilli and the presence of *Gardnerella vaginalis* and representatives of fecal flora, in particular bacteria of the family *Enterobacteriaceae* with dominating *Escherichia coli*, as well as gram-negative anaerobes *Bacteroides spp*. and enterococci. The frequency occurrence of certain types of staphylococci varies: the rate of *S.epidermidis* and *S.haemoiyticus*, able to act as pathogens, especially in case of local immunodeficiency, increases. The substitution of *C.genitalium* and *C.pseudogenitalium* by pathogenic *C.minutissimum* is observed in the semen of patients with chronic prostatitis. Riegel et al. isolated a new species of pathogenic corynebacteria, *C.seminale sp. nov*, from the semen of infertile men [21,22,23,24].

Therefore, it is obvious that representatives of human autoflora are the main pathogens of male urogenital infections that result in pathospermia development. Most researchers believe that specific features of the species spectrum of the ejaculate microflora in infertile patients and the isolation of the prostate and seminal vesicles from the environment allow to relate a certain part of male infertility cases to a pathology resulting from purulent inflammatory processes in the genitourinary tract with predominantly endogenous infection sources [25,26].

GRAM-POSITIVE PATHOGENS OF THE UROGENITAL TRACT ASSOCIATED WITH INFERTILITY

Since representatives of the genus *Staphylococcus* are among the most frequently identified groups of bacteria in the semen of subfertile men, we think their biological profile is of considerable interest. These staphylococci are characterized by evident adhesion and the ability to bind some surface proteins of eukaryotic cells (laminin, fibronectin, vitronectin, collagen) [6], which contributes to the development of ascending infection of the urogenital tract and prostate colonization. In addition, they produce a slime substance with antiphagocytic, antichemotactic and antiproliferative properties, which has a damaging effect on neutrophils and lymphocytes. The possibility of long-term persistence of coagulase-negative staphylococci in regions of the urogenital tract (as in many other organs) apparently determines their ability to inactivate lysozyme, the complement and platelet membranotropic antimicrobial protein belonging to the defensins [27,28,29].

As far back as in 1969, G.N. Chistovich suggested singling out the following categories of individuals by duration of carriage of pathogenic staphylococci:

- permanent carriers of the resident type ("persistent") with constant and considerable secretion of staphylococcus of the same phagotypes with multiple drug antibiotic resistance;
- permanent carriers of the transient type with constant secretion of pathogenic staphylococcus, but their phagotypes and quantity vary;
- temporary carriers that do not secrete pathogenic staphylococci constantly, and their phagotypes and quantity vary;
- individuals that are constantly free of staphylococci [6].

It makes sense to dwell on some epidemiologically significant properties of such "persistent" microorganisms in more detail.

Currently, a correlation between the degree of anti-lysozyme activity (ALA) of staphylococci and different types of carriage has been established; it is associated with the intensity of bacterial intracellular reproduction and the duration of persistence. Strains with high ALA were more often secreted from the resident bacteria carriers. Its presence provides the bacteria with additional survival mechanisms, facilitating the clearance of the niche in conditions of intracellular parasitism. The mere fact that ALA was detected in microorganisms of this species allows us to classify it as a resident representative. The vast majority of "carrying" epidermal staphylococci were concentrated in the group with ALA ranging from 3.0 to 4.5 µg/ml. Therefore, when ALA is less than this value, we can only speak of transient carriage [6].

The normal level of lysozyme in the ejaculate of healthy men is about 6.0 mcg/ml (4.5-7.2 mcg/ml), while the one of prostatitis patients is about 0.73 mcg/ml (0.4-1.2 mcg/ml). The widespread and pronounced ALA ensures that microorganisms can survive in the host for a long time. At the same time, persistence of bacteria capable of inactivating lysozyme appears to form a lysozyme deficiency in the sperm. Along with this indicator, other markers that allow to efficiently identify microorganisms that are "responsible" for the development of subfertility have been described. They are all associated with the ability of pathogens to degrade various factors of anti-infectious resistance and produce a number of exometabolites that bind or destroy these factors and affect the immune response regulation systems [30,31,32].

These properties of microorganisms mainly include adhesive, ribonuclease, anti-immunoglobulin, anti-lactoferrin, and lipase activities. The ability of bacteria to synthesize substances structurally similar to human neopterin, lactoferrin and alpha-1 antitrypsin is also of absolute interest [3].

On the other hand, many persistent microorganisms are capable of stimulating the production of pro-inflammatory cytokines, activating cascade mechanisms of production of mediator molecules that disorganize the cellular arm of the immune response, and thus maintaining the chronic inflammation site. This process leads to degenerative changes in various organs of the reproductive tract and the development of pronounced microflora disorders [33,34,35].

GRAM-NEGATIVE PATHOGENS OF THE UROGENITAL TRACT ASSOCIATED WITH INFERTILITY.

The next group of microorganisms widely represented in human semen are enterobacteria. *E.coli* is the dominant enterobacterium secreted from the semen of infertile men. These isolates are characterized by certain properties similar to the uropathogenic variants of *Escherichia* (UTI groups): the presence of certain O-K antigens (04, 06, K1, K5), hemolysins and cytotoxic necrotizing factor (CF-1), causing alteration of the reproductive tract tissue and having direct spermicidal action. At the same time, these *E.coli* isolates are characterized by resistance to many antibiotics and the presence of specific T1F+P fimbriae that show a high degree of ligand-receptor binding to the acrosome of spermatozoa, which causes their agglutination. It is likely that this combination of pathogenicity markers characterizes *E. coli* that are tropic to the tissues of the male urogenital tract and can be designated as the urogenital group of *Escherichia* [36]. Colonizing the urogenital tract epithelium, pathogenic *E. coli* cause the release of certain cytokines (IL 6,8,1a, TNF-ɑ), mediated by the structural components of the *E. coli* cell wall – lipopolysaccharide (LPS) and PapG adhesion – which specifically bind to glycosphingolipids of eukaryotic membranes [6]. IL 1 and IL 8 stimulate polymorphonuclear neutrophils which in their turn induce production of reactive oxygen radicals; oxidizing phospholipids of sperm membranes, these radicals cause their death. It was found that the pathogenic strains of *E.coli* are able to bind TNF-ɑ, which can increase their invasive properties, and cytokine sorption on bacterial cells can lead to dysregulation of the immune response, facilitating the persistence of *E. coli*. Pathogenic enterobacteria express mitochondrial and cytoplasmic proteins GroEL (60 kDa) and GroES (15 kDa), increasing their resistance to lysosomal enzymes and active oxygen radicals of phagocytes, which finally leads to incomplete phagocytosis resulting in the persistence of *E. coli* and the development of local immunodeficiency. *Escherichia* persistence can be also favoured by capsule synthesis (K1, K5 antigens), defensin resistance, secretion of catalases and proteases with different specificity which cause sperm agglutination and destroy lysozyme, immunoglobulins and different fractions of the complement. On the other hand, prolonged persistence of *E.coli* has a modifying effect on intracellular metabolism of the urogenital tract cells by stimulating the expression of Hsp 60 proteins with macrophages and endothelial cells, which results in a cross-immune response manifested through the formation of antispermatic antibodies. It is also known that Hsp 70 affects metabolism in germinal cells and, in particular, decreases testosterone production [37, 38].

NATURAL RESISTANCE AGAINST INFECTIONS OF THE MALE REPRODUCTIVE TRACT

It is known that the development of an infectious process requires a certain background – the state of reactivity and resistance of the organism. At the same time, implementation of the second principle for diagnosing chronic infection development (detection of changes in the organism exposed to the pathogen) is not widespread due to the lack of reliable information tests in the deviation of the immune status in case of carriage. There are only a few references on this issue [6, 39,40,41].

Until recently, peripheral blood and serum were the only materials used to study the human immune system. At the same time, there is undeniable evidence that the abnormal focus causes the greatest changes of immunological and biochemical markers in the place of its localization, as well as data on the greater informativeness of determining certain immunity indicators in various body fluids in immunopathological conditions. It is due to the fact that in the focus of inflammation, immune competent cells acquire features of activated cells; the antigens and receptors expressed and the cytokines produced in them differ from the ones in circulating blood cells [42,43,44,45,46]. Therefore, determining the state of natural resistance factors directly in sperm gives high research reliability, since the value of these indices is less affected by the focus of inflammation of any other localization [47,48,49,50,51].

Bactericidal activity of sperm, which can be referred to the complex factors of natural resistance that control the survival of bacteria in the urogenital tract, should be considered one of the promising indicators reflecting the condition of the male reproductive system. It was found that sperm had bactericidal properties, although not in all the examined patients. Sperm significantly suppressed the growth of the test culture of *E. coli* standard strain compared to the control only in 50% of patients [52].

It was found that the sperm of young men – donors aged 32 and younger – has the highest bactericidal activity. In this case half (or more) of the test culture cells were inactivated in 70.1 % of cases, while high bactericidal activity of sperm among donors over 32 was recorded only in 35.7 % of cases. However, it cannot be claimed that bactericidal activity of sperm disappears with age at all. It is present with approximately equal probability in both age groups: in 46.5% of donors aged 32 or younger and in 56.0% of older donors. Therefore, the bactericidal activity of sperm is preserved in older age groups, but the activity of immunological and biochemical systems providing it appears to be gradually decreasing [52].

Patients whose semen viscosity exceeded 6.5 cm had no bactericidal properties. As semen viscosity depends on the functional state of the prostate, we can conclude that bactericidal activity of sperm is also provided to some extent by the substances produced by it. In our opinion, a certain role in the bactericidal activity is played by such antibacterial substances as lactoferrin – its main place of synthesis in the male reproductive system is the prostate and seminal vesicles – and spermine produced by the prostate gland. It is believed that spermine helps preserve the secretion pH, specifying its antimicrobial properties. However, in a number of studies, patients with high sperm viscosity and absence of BAS had pH values within normal limits ranging from 7.4 to 7.5 [45].

Antimicrobial activity of the prostate is explained by the presence of free zinc in it; moreover, the prostate secretion contains various enzymes (acid and alkaline phosphatases, proteinases, lactate dehydrogenase, diamine oxidase, cholinesterase, catalase, glutamic oxaloacetic transaminase, aconitase) which are produced directly by its glandular epithelium [13,19,22,41]. As the prostate gland significantly changes with age, which comes together with changes in its functional activity, the revealed changes in BAS level seem rather logical.

Research that has been carried out over recent years in the field of clinical and experimental medicine, including urology and andrology, medical microbiology, biochemistry and other allied disciplines, has increased clinicians' attention to I.I. Mechnikov's idea about a leading role of microorganisms living in the human body in health maintenance and disease occurrence, though the answer to the key question of medicine of all times on why diseases happen and how they start still remains relevant and requires out-of-the-box approaches and solutions, and we made an attempt to outline directions of some of them in the present paper.

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