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Видавнича група

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Журнал заснований з метою розвитку наукового потенціалу та реалізації кращих традицій науки в Україні, за кордоном. Журнал висвітлює історію, теорію, механізми формування та функціонування, а, також, інноваційні питання розвитку медицини, психології, педагогіки та. Видання розраховано на науковців, викладачів, педагогів-практиків, представників органів державної влади та місцевого самоврядування, здобувачів вищої освіти, громадсько-політичних діячів.

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CHRONIC INFLAMMATORY PROCESS OF THE GENITOURINARY SYSTEM IN WAG RATS POPULATION: DEVELOPMENT OF OWN MODELING METHODOLOGY

Abstract. Experimental models of the urogenital chronic infection process are keys to studying the mechanisms of the pathogenesis of development of kidneys pathology in the offspring, which is associated with the infection of women during pregnancy or even before pregnancy with the determination of the trigger factors for the development of the inflammatory process.

Aim. The aim of research was to develop an experimental model of genitourinary system chronic inflammatory process in sexually mature female rats of the WAG population, caused by Proteus mirabilis and Streptococcus pyogenes, taking into account the ability to form biofilms, as a leading factor in the pathogenicity of these pathogens.

Material and methods. 8 months aged sexually mature female rats of the WAG population weighing 200-300 grams were divided into three groups for the experiment. Microbiological and morphological methods were used. The material for morphological research was the kidneys of rats from the control and experimental groups. The morphometric method was used to objectify the results of the study. The width of nephrogenic zone of cortical layer in newborn rats, the width of cortical layer and the numerical density of glomeruli in all age categories were determined in kidney preparations stained with hematoxylin and eosin by videomicroscopic morphometry using the Olympus DP-Soft program (Version 3:1) and the produced micropreparations were examined using ZEISS Primostar 3 microscopes (Carl Zeiss, Germany) with a built-in color digital camera, BRESSER Science TFM-301 Trino with a BRESSER Full HD camera (Bresser GmbH, Germany).

Results. The chronic inflammatory process of the genitourinary system was reproduced by transurethral and vaginal administration of a daily biofilm form of

Proteus mirabilis uroisolate (I group of rats) and Streptococcus pyogenes uroisolate (II group of rats) in 0.2 ml once a day three days in a row. On 10th day there was once injected intraperitoneally reference strains of Proteus mirabilis in group I rats, and Streptococcus pyogenes in group II rats. On the 19th-22nd day after planting the male rats, the female rats gave birth to offspring. In micropreparations of genitourinary system organs of both groups rats general pathological inflammatory processes of various nature were found: morphological study revealed vaginitis, cervicitis, endometritis and myometritis, oophoritis in chronic form together with chronic urethritis, chronic cystitis and chronic pyelonephritis.

Conclusions. This original method of modeling of genitourinary system chronic inflammatory process should be used when studying the development of pathological processes in offspring born from mothers with pathology of urogenital tract.

Keywords: biofilms, chronic inflammatory process of the genitourinary system, experiment on rats, uroisolates, morphological study.

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ХРОНІЧНИЙ ЗАПАЛЬНИЙ ПРОЦЕС СЕЧОСТАТЕВОЇ СИСТЕМИ У ЩУРІВ ПОПУЛЯЦІЇ WAG: РОЗРОБКА ВЛАСНОЇ МЕТОДИКИ МОДЕЛЮВАННЯ

Анотація. Експериментальні моделі хронічного інфекційного процесу сечостатевої системи є ключовими для вивчення механізмів патогенезу розвитку патології нирок у потомства, що пов'язано з інфікуванням жінок під час або до вагітності, з визначенням тригерних факторів розвитку запального процесу.

Мета. Метою дослідження була розробка експериментальної моделі хронічного запального процесу сечостатевої системи у статевозрілих самок щурів популяції WAG, спричиненого уроізолятами *Proteus mirabilis* та *Streptococcus pyogenes*, з урахуванням здатності до утворення біоплівок, як провідного фактора патогенності збудників.

Матеріали та методи. В експерименті було використано статевозрілі щури-самиці популяції WAG у віці 8 місяців масою 200 грамів. Усі тварини були розділені на три групи. Використовували мікробіологічні та морфологічні методи. Матеріалом для морфологічного дослідження були нирки щурів контрольної та дослідних груп. Для об'єктивізації результатів дослідження використовували морфометричний метод. Виготовлені мікропрепарати забарв-

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лювали гематоксиліном та еозином та досліджували за допомогою відеомікроскопічної морфометрії з використанням програми Olympus DP-Soft (версія 3:1) та за допомогою мікроскопів ZEISS Primostar 3 (Carl Zeiss, Німеччина) з вбудованою кольоровою цифровою камерою, BRESSER Science TFM-301 Trino з камерою BRESSER Full HD (Bresser GmbH, Німеччина).

Результати. Хронічний запальний процес сечостатевої системи відтворювали шляхом трансуретрального та вагінального введення щоденної біоплівкової форми уроізоляту *Proteus mirabilis* (I група щурів) та уроізоляту *Streptococcus pyogenes* (II група щурів) по 0,2 мл один раз на день три дні поспіль. На 10-й день одноразово внутрішньочеревно вводили референтні штами *Proteus mirabilis* щурам I групи та *Streptococcus pyogenes* щурам II групи. На 19-22-й день після підсадки самців, самиці народжували потомство. У мікропрепаратах органів сечостатевої системи обох дослідних групах щурів було виявлено загальні патологічні запальні процеси різної природи: морфологічне дослідження виявило вагініт, цервіцит, ендометрит та міометрит, оофорит у хронічній формі разом із хронічним уретритом, хронічним циститом та хронічним пієлонефритом.

Висновки. Цей оригінальний метод моделювання хронічного запального процесу сечостатевої системи доцільно використовувати при вивченні розвитку патологічних процесів у потомства, народженого від матерів з патологією урогенітального тракту.

Ключові слова: біоплівки, хронічний запальний процес сечостатевої системи, експеримент на щурах, уроізоляти, морфологічне дослідження.

Problem statement. Chronic genitourinary system infections, especially during pregnancy, belong to a very common pathology and cause significant negative effect on the health of pregnant woman and child even before birth and, as a result, to the development of nephropathology in the offspring. These diseases are characterized by a long course, which is the result of pathogen’s persistence associated with antimicrobial polyresistance. At the same time, historically formed in medical practice approaches to the treatment of acute and chronic forms of the same infectious pathology differ little from each other. This is a factor that requires a review of some principles in treatment based on modern concept of pathology and pathophysiology of infectious process. The most important role of microbial factor in pathogenesis of chronic and recurrent genitourinary tract infection is absolutely confirmed today, as each pathogen has its own pathogenicity and virulence factors that determine the development and form of pathological process during pregnancy. Ignoring the laws of the interaction between micro- and macroorganisms or microorganism itself with medical drugs, leads to the appearance of resistant to antimicrobial therapy forms of microorganisms, these also affect the state of immune reactivity of a pregnant woman. Such situations, as a rule, are one of the main reasons for the formation of nephropathology in the fetus associated with the main disease in pregnant woman,

which significantly complicates the course of disease, worsening its prognosis. At the same time, the key role in the chronicity of genitourinary tract infections is played by the pathogenic properties of microorganisms, especially in associations represented by gram-positive and gram-negative pathogens. Therefore, the specific properties of the microbial agent are of key importance in the evolution of infectious diseases accompanied by the chronicity of a typical pathological process.

At the same time, high indicators of the duration of hospitalization and the insufficient degree of antimicrobial therapy effectiveness indicate the necessity of improving the standards of medical care for pregnant women with chronic genitourinary tract infections and introduction of more effective diagnostic methods, primarily in people who belong to the group of high risk of developing chronic kidney disease.

The most serious complication of a chronic genitourinary tract infection is the transmission of infection to the fetus with the development of intrauterine infection, which after birth can be realized in various variants of infectious and inflammatory diseases of newborns, in particular, the development of nephropathology. A characteristic feature of intrauterine infection during pregnancy is the impossibility of its clear diagnosis. There are only indirect signs by which one can assume the presence of such infection, but even the absence of these signs in the antenatal period does not exclude the realization of intrauterine infection among newborns. Treatment of intrauterine infection is sometimes associated with the need for resuscitation measures, with the participation of highly qualified medical personnel and large economic costs. Due to these circumstances, the detection of a chronic variant of the course of genitourinary tract infection requires the appointment of antibacterial therapy.

The available data does not sufficiently cover the results of research devoted to finding ways to optimize nephrological care for pregnant women based on pathophysiological reasoning. Therefore, studying the pathophysiological features of genitourinary pathology, especially during pregnancy, is extremely needed. All this determines the relevance and necessity of developing an experimental model that maximally reflected all links of the pathogenesis of the chronic course of genitourinary infection in pregnant women to improve the quality of specialized medical care for such category of patients.

Analysis of recent research and publications. Urogenital tract infection in women is the most common multifactorial infection and up to 80 % of these infections are associated with the use of urethral catheters [4, 7] and spirals against fertilization, which are exposed to the complex dynamic environment of urine and vaginal secretions flow with the development of a chronic infectious process, which is associated with the formation of dense biofilms by microorganisms, the causative agents of the inflammatory process. A crucial part of urogenital infection pathogenesis in women of fertile age is the formation of a bacterial biofilm on the surface of biomaterials, which can lead to persistent resistance [10] of microbial biofilms and suppression of immunity, which leads to chronic inflammation and, as a result, affects the

development of intrauterine infection [5]. Experimental models of the urogenital chronic infection process are keys to studying the mechanisms of the pathogenesis of development of kidneys pathology in the offspring, which is associated with the infection of women during pregnancy or even before pregnancy with the determination of the trigger factors for the development of the inflammatory process.

Simulation of the pathological process in laboratory animal models is usually used in biomedical research as a basis for experimental hypotheses in pathological physiology [9]. The use of animal models is an extremely important experimental method and tool in modern biomedical research, which contributes to a more convenient and effective understanding of the patterns of development of human diseases, in particular, the urogenital tract of pregnant women [17]. As experimental animals, white rats are most often used, because they have the closest to human type of relationship between maternal and fetal blood circulation, the morphofunctional structure of the placenta and the placental barrier between the rat and human organisms are close to identity. Therefore, the use of white rats as laboratory animals allows us to extrapolate the results of the experiment [2]. In the specialized literature, there are reports on the simulation of urogenital system inflammatory process, but these models were heterogeneous, the most common infectious agents in modeling of acute urogenital pathology in laboratory animals were *Escherichia coli* and *Proteus mirabilis* in the planktonic form of culturing. [22].

In this regard, the development of an optimal model of the chronic inflammatory process in the genitourinary system, devoid of infliction of surgical trauma on animal and at the same time as close as possible to real clinical conditions, remains an urgent task of experimental medicine today.

The aim of research was to develop an experimental model of genitourinary system chronic inflammatory process in sexually mature female rats of the WAG population, caused by *Proteus mirabilis* and *Streptococcus pyogenes*, taking into account the ability to form biofilms, as a leading factor in the pathogenicity of these pathogens for study the percularities in pathgenesis of genitourinary system infections.

Material and methods. Pathogens of genitourinary system infections were isolated from 89 pregnant women who were hospitalized at the Communal Non-Commercial Enterprise of the Kharkiv Regional Council "Regional Clinical Perinatal Center". The vast majority of cases of urogenital infections were asymptomatic bacteriuria (n=29) and chronic pyelonephritis (n=26). *Proteus mirabilis* (10 uroisolates) and *Streptococcus pyogenes* (7 uroisolates) were found among the leading causative agents of chronic pyelonephritis, 11 *Proteus mirabilis* uroisolates and 2 strains of *Streptococcus pyogenes* were isolated in asymptomatic bacteriuria.

Urine samples were taken for microbiological research on the day of hospitalization of pregnant woman before the start of treatment and delivered to the laboratory in compliance with generally accepted requirements and rules [1]. The results of microbiological examination were interpreted based on the counting of bacterial colonies. Detection of $5x10^4$ CFU/ml in urine samples obtained during

catheterization or $1x10^5$ CFU/ml in samples of the average portion of morning urine gave opportunity to diagnose an infection of urinary tract. Microorganisms were identified using the MICRO-LA-TEST® kits (ErbaLachema, Czech Republic) for standard identification using micromethods. Preparation of suspensions of microorganisms with a certain concentration of microbial cells was carried out using an electronic device Densi-La-Meter (PLIVA-Lachema a.s., Czech Republic) according to the instruction of the device. Optical density was measured using a Multiskan EX microplate spectrophotometer (type 355). Synchronization of periodic cultures of uroisolates was carried out after establishing the growth kinetics of the asynchronous culture. The regime of periodic cultivation was determined in such a way that during exponential growth the cell mass increased from two to five times (under cold conditions). Density of formed biofilms was carried out by determining the ability of bacterial strains to adhere to the surface of a polystyrene plate, the result was expressed in conventional units of optical density. Sterile polymer Petri dishes with a diameter of 40 mm were used to visualize biofilms [14]. Microscopy was carried out using a “Granum” microscope with oil immersion.

The experimental study was conducted on the basis of the experimental biological clinic of the Kharkiv National Medical University. 8 months aged sexually mature female rats of the WAG population weighing 200-300 grams were used in the experiment. All animals were divided into three groups. Group I included 72 animals, in which there was simulated a genitourinary system chronic inflammatory process caused by *Proteus mirabilis*. The II group included 72 animals with modeled genitourinary system chronic inflammatory process caused by *Streptococcus pyogenes*. Group III included 24 intact female rats that were not subjected to any manipulations. The experiment was repeated two times more. The experimental study was conducted in accordance with the “General Ethical Principles of Animal Experiments”, which were approved by the III National Congress (Kyiv, 2007) and in accordance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes” (Strasbourg, 1986).

For morphological study genitourinary system organs of rats were taken. The material was fixed in a 10 % formalin solution. Sealing of formalin-fixed tissues was achieved by passage through alcohols of increasing concentration, Nikiforov's solution (96 % alcohol and diethyl ether in a ratio of 1:1), chloroform, and embedding in paraffin. From the manufactured blocks, serial sections with a thickness of $4\text{-}5\times10^{-6}$ m were made for subsequent staining with hematoxylin and eosin. The width of nephrogenic zone of cortical layer in newborn rats, the width of cortical layer and the numerical density of glomeruli in all age categories were determined in kidney preparations stained with hematoxylin and eosin by videomicroscopic morphometry using the Olympus DP-Soft program (Version 3:1) and the produced micropreparations were examined using ZEISS Primostar 3 microscopes (Carl Zeiss, Germany) with a built-in color digital camera, BRESSER Science TFM-301 Trino with a BRESSER Full HD camera (Bresser GmbH, Germany).

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Presentation of the main material. Based on the results of previous studies [12], in which my colleagues and I established that the leading pathogens of genitourinary tract infections in pregnant women of the Kharkiv region were *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Streptococcus pyogenes, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa*, among which, in cases of chronic pyelonephritis, the first place was occupied by *Proteus mirabilis* (10 cases, 38.5 %), the 2nd place was in *Streptococcus pyogenes* (7 cases, 26.9 %), *Escherichia coli* (4 cases, 15.4 %) and *Proteus vulgaris* (4 cases, 15.4 %) were on third place. In women with asymptomatic bacteriuria among etiological factors, *Proteus mirabilis* (11 cases, 37.9 %) was first, as the second one was *Escherichia coli* (8 cases, 27.6 %), and the third – *Proteus vulgaris* (3 cases, 10.3%) and *Enterococcus faecalis* (3 cases, 10.3%). In addition, *Streptococcus pyogenes* has a special phenomenon - antigenic mimicry with antigens of glomerular nephron cells, which leads to the development of an autoimmune process, and this may contribute to the chronic course of genitourinary tract infection.

It is known that in all proteus infections, *Proteus mirabilis* dominates in 80-90 % of cases, and urinary tract infections, mainly ascending, associated with the use of urological catheters (catheter-associated urinary tract infections) ways). These infections often occur in patients with long-term catheterization of the urinary tract, in particular, with exacerbation of chronic infection of genitourinary tract in pregnant women.

The development of genitourinary tract infection, in particular the chronic form, is caused by the continuous action of pathogenicity factors of pathogens, the leading one of which is the ability to form biofilms, which are mobile communities that protect bacteria from the negative effects of environmental factors. As the ability to form biofilms, capable of forming new planktonic cells, also able of forming new (secondary) biofilms, is a factor in the adaptation and colonization of microorganisms, therefore *Streptococcus pyogenes* and *Proteus mirabilis* isolates, which formed the thinnest biofilms, were chosen for modeling the experimental infection.

Therefore, during the development of the method of reproduction of chronic infectious process of genitourinary tract, two leading urological strains were chosen, *Streptococcus pyogenes* from gram-positive bacteria, and *Proteus mirabilis* from gram-negative bacteria, as both had the highest degree of pathogenicity and virulence with a high density of formed biofilms.

The genitourinary system chronic inflammatory process was reproduced by administration with the help of transurethral and vaginal catheter (catheter 3FR/1.0*130mm. Code:00003, buster, Germany) into the bladder and vagina 0.2 ml of a daily broth culture of uroisolates of *Proteus mirabilis* and *Streptococcus pyogenes*, which were isolated from pregnant women with a chronic urogenital process. For the experimental study, uroisolates that had the greatest ability to form dense biofilms were selected (fig. 1): *Proteus mirabilis* formed biofilms with optical density of 3.86 units (fig. 1a-b), and *Streptococcus pyogenes* formed biofilms density was 4.48 units (fig. 1 c-d).

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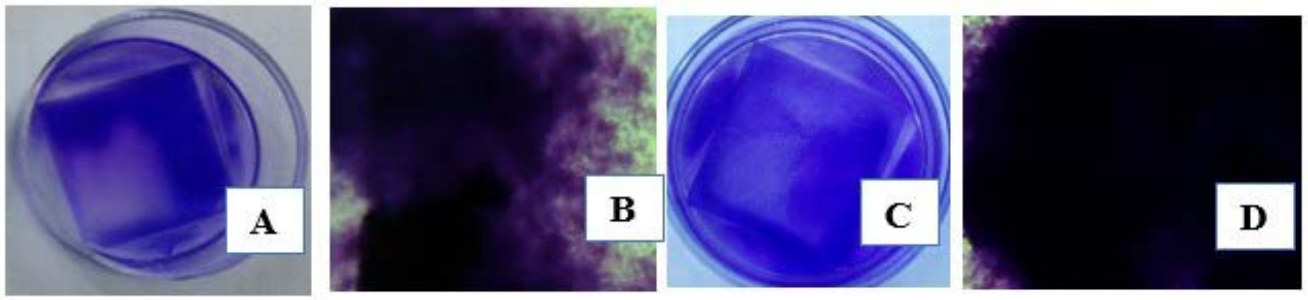

Fig. 1. Formation of dense biofilms of Proteus mirabilis (A, B) and Streptococcus pyogenes (C, D). Microscopy of biofilms was performed with microscope "Granum" with oil immersion. Digital i mages of biofilms of uroisolates prepared with video eyepiece "ToupCam 3.1".

To perform bladder catheterization, a female rat was immobilized on its back, which was accompanied by the act of urination. This indicated that the bladder appeared empty and allowed a certain volume of liquid to be introduced into it. In order to avoid the initiation of repeated reflex urination in the rat due to irritation of the thermoreceptors of the bladder wall, the temperature of the syringe, its contents (bacterial culture) and the catheter are maintained using a thermostat at the temperature of the rat's internal organs (37^0C). In addition, in order to avoid irritation of the mechanoreceptors of the bladder wall with the initiation of repeated reflex urination, a small volume of liquid is used - 0.1 ml per 100 g of the rat's body weight, i.e. 0.2 ml. A similar dose was injected into the genital tract.

Proteus mirabilis uroisolate at a concentration of 10^8 CFU/ml was administered to the I group animals, and *Streptococcus pyogenes* uroisolate at a concentration of 10^6 CFU/ml to the II group once a day three days in a row. A day after the third administration of uroisolates, a urine study was conducted, during which the rats of both groups showed inflammatory changes characteristical for urinary tract infections (bacteriuria and alkaline reaction), which persisted throughout the experiment (table I).

On the 10^{th} day of the experimental study intraperitoneally once *Proteus mirabilis* reference strain (SS F403) at a concentration of 10^{10} CFU/ml was injected to group I rats and *Streptococcus pyogenes* reference strain (IBC № 1) at a concentration of 10^8 CFU/ml was injected to group II animals.

On the 20^{th} day of the experiment, female rats of all groups were planted with male rats (1 male to 4 females). On the 19^{th}-22^{nd} day after planting the males, the females gave birth to offspring. For further comprehensive morphological study, 8 females that gave birth to offspring were taken out from each group.

During microscopy, in groups I and II, in the mucous and muscular membranes of the vagina, cervix and uterus, in the ovaries, a moderately pronounced focal-diffuse polymorphic cellular infiltration was registered, represented by lymphocytes, macrophages, plasma cells, single neutrophils and eosinophils, which indicated the development of intermediate (interstitial) inflammation, which is known to be one of the types of productive (chronic) inflammation (fig. 2, fig. 3).

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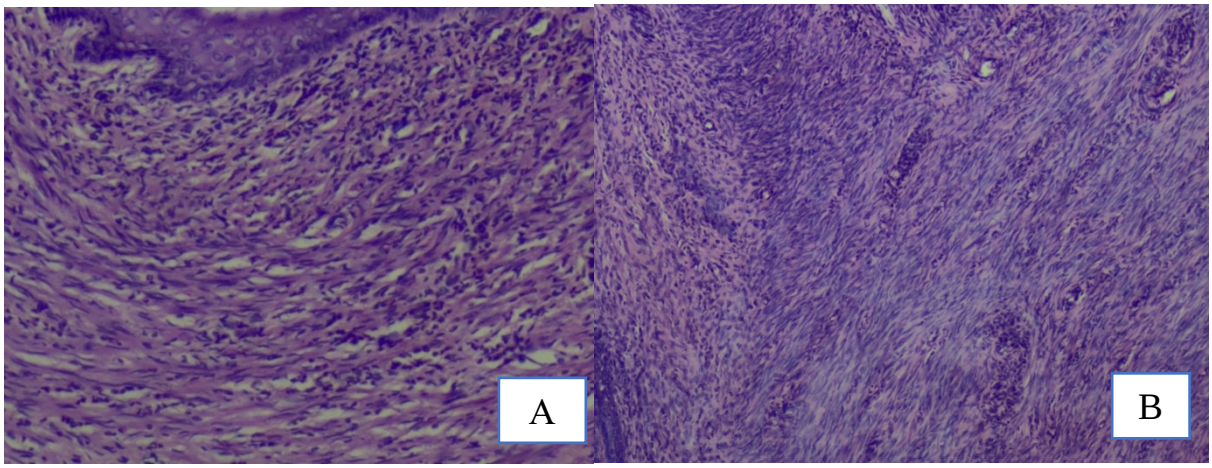

Fig. 2. Focal moderate sclerotic changes and diffuse polymorphic inflammatory cell infiltration in the muscular membrane of the cervix of a female group I (A) and the uterus of a female rat of group II (B). Staining with hematoxylin and eosin, A) ×200, B) ×100.

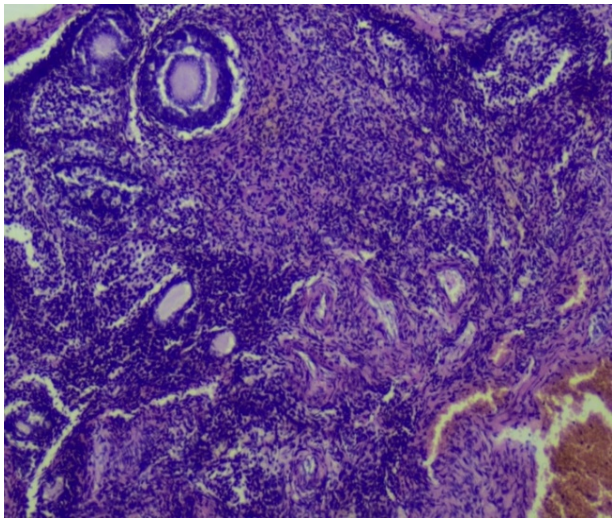

Fig. 3. Diffuse polymorphic inflammatory cell infiltration, sclerotic and hemodynamic disturbances, decrease in the number of follicles in the ovary of group II rats. Staining with hematoxylin and eosin, ×100.

On background of inflammatory changes in the vagina, cervix, uterus, and ovaries, focal moderately expressed sclerotic changes and hemodynamic disturbances, represented by edema, full blood vessels, and the formation of small focal hemorrhages, were detected. A decrease in the number of follicles was found in the ovaries of groups I and II rats compared to the ovaries of group III rats that indicates a decrease in the ovarian reserve and may lead to a decrease or complete loss of fertility [5, 21].

During the study of micropreparations in the organs of the urinary system of groups I and II rats various general pathological processes were also detected. Thus,

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focal alterative-desquamative and inflammatory changes were detected in the ureters, urinary bladder and urethra in the epithelial layer, which were characterized by the presence of polymorphic cellular infiltration represented by lymphocytes, macrophages, plasma cells, single neutrophils and eosinophils. In the lamina propria of the mucous membrane, the submucosa, the muscular and serous membranes of the specified organs, moderate focal sclerotic changes, signs of blood circulation disorders manifested by edematous changes, full blood vessels and small focal hemorrhages, polymorphic inflammatory cellular infiltration were found (fig. 4).

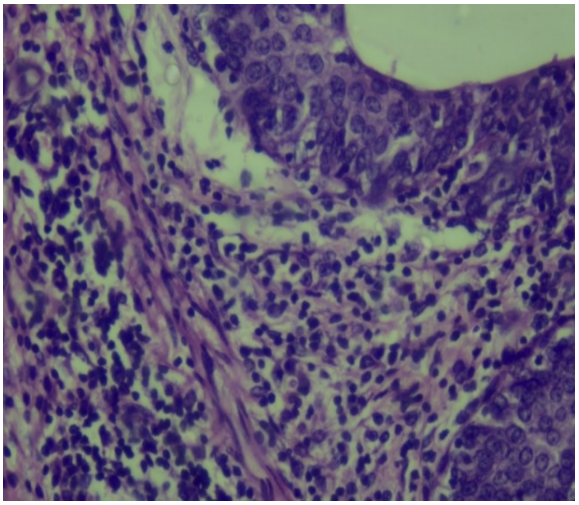

Fig. 4. Inflammatory polymorphic cellular infiltration in the mucosa and submucosal base of the ureter of group I female rats. Staining with hematoxylin and eosin, ×400.

The latter was diffuse in the lamina propria of the mucous membrane, submucosal base, muscle layer, focal in the serous membrane and was characterized by the presence of lymphocytes, macrophages, plasma cells, single neutrophils and eosinophils.

In groups I and II rats compared with group III, an increase in the number of visual fields with the presence of focal clusters of immune cells in the mucous membrane of the ureter and bladder was found. The latter, as is known, refer to lymphoid tissue associated with mucous membranes, which carries out local protective reactions [8].

In the cortical and medullary layers of the kidneys of groups I and II rats general pathological processes of various nature were detected in both the parenchymal and stromal components of the kidneys (fig. 5, fig. 6).

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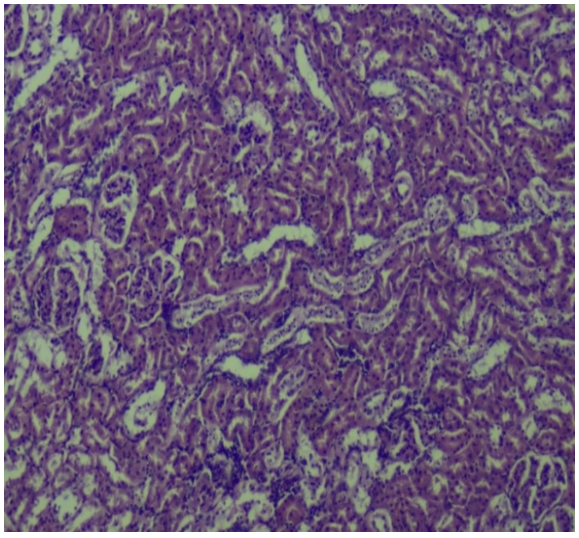

Fig. 5. Polymorphic inflammatory cell infiltration in the glomeruli with proliferation of endothelial and mesangial cells, thickening of some capillary net walls, single formation of "lobularity". Periglomerular sclerosis in part of glomeruli. Alterative changes in the tubule epithelium. Focal inflammatory cell infiltration in the stroma of the rat kidney of group I. Staining with hematoxylin and eosin, ×100.

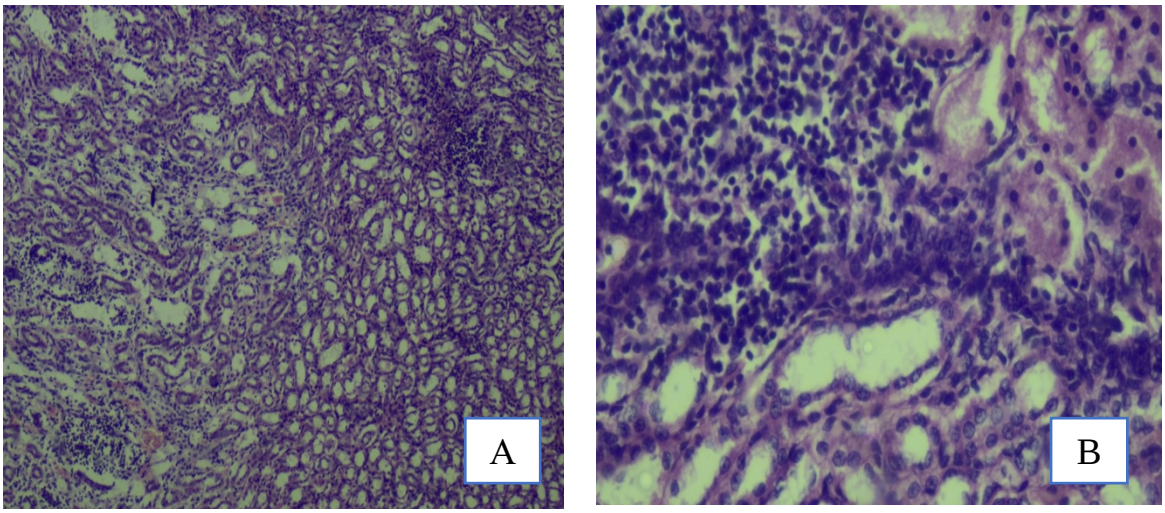

Fig. 6. Dystrophic-necrotic changes in the tubule epithelium; sclerotic changes, hemodynamic disturbances, diffuse inflammatory polymorphic cell infiltration in the stroma of the rat kidney of group I (A) and group II (B). Staining with hematoxylin and eosin, A) ×100, B) ×400.

Polymorphic inflammatory cell infiltration was found in the glomerular apparatus of the kidneys, represented by lymphocytes, macrophages, plasma cells, single neutrophils and eosinophils; moderately pronounced or pronounced proliferation of endothelial and mesangial cells; thickening of capillary net walls; the formation of "lobularity". Periglomerular sclerosis with inflammatory polymorphic cellular infiltration was also found around some glomeruli.

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Moderate dystrophic-necrotic changes of epitheliocytes were noted in the tubular apparatus of the kidneys. The lumens of some tubules looked expanded with the presence of eosinophilic colloidal masses in them. In the latter, the epithelium was atrophied.

Moderate sclerotic changes were detected in the renal stroma; hemodynamic disturbances, represented by edema, full blood vessels and small focal hemorrhages; inflammatory polymorphic cellular infiltration. The latter was focal in the cortical layer, diffuse in the cerebral layer and was characterized by the presence of lymphocytes, macrophages, plasma cells, single neutrophils, and eosinophils. Some vessels of the stroma had a thickened wall due to sclerotic changes.

Moderate sclerotic changes, hemodynamic disturbances and diffuse polymorphic inflammatory cell infiltration, represented by lymphocytes, macrophages, plasma cells, single neutrophils and eosinophils, were found in the wall of pelvis and calyx.

So, in rats of groups I and II, the morphological study revealed chronic vaginitis, chronic cervicitis, chronic endometritis and myometritis, chronic oophoritis in the organs of the reproductive system, and chronic urethritis, chronic cystitis, chronic ureteritis and chronic pyelonephritis in the organs of the urinary system. In order to confirm the development of genitourinary system chronic infection, the causative agents of the inflammatory process introduced into the genitourinary tract were identified. With the help of the method of prints on the surface of nutrient medium, the uterine wall, placenta and kidney were inoculated. Seeding of amniotic fluid was carried out by rubbing into the surface of nutrient medium. As a result, those causative agents of the inflammatory process were identified, which were introduced into the urogenital tract to reproduce the chronic inflammatory process and were sown at the end of pregnancy from the kidney. Taking into account the method of infection, this indicates the localization of the infectious center of inflammation in the urinary tract. Sowing pathogens from the fetoplacental system (placenta and amniotic fluid) reflects the implementation of the process of intrauterine infection of the fetus. Identification of microorganisms introduced into the urinary bladder and genital tract, and sown from the kidney and fetoplacental complex, proves the interrelationship of these processes.

DISCUSSION. Exacerbation of a chronic genitourinary tract infection is one of the most common pathologies during pregnancy. In turn, pregnancy itself negatively affects the course of the chronic inflammatory process in the organs of the genitourinary tract.

Difficulties in the treatment of exacerbation of chronic pyelonephritis during pregnancy are associated with a number of factors, such as the development of urinary tract obstruction, the high virulence of gram-negative and gram-positive microflora that causes the disease, polyresistance of this flora to antibacterial drugs due to the formation of dense biofilms [16, 20].

The presence of pathogens in the urine and proteinuria increase the adhesion of salts to catheter surface. Additionally, infecting of catheter with antibiotic-resistant

bacterial associations that form dense biofilms is due to the adhesive factors of the uropathogens themselves. Microbial colonization of catheter can develop within hours or days, but the risk increases with the length of time the catheter remains in the ureter, especially for mixed infections. The formation of biofilms can nullify correctly selected modern antibacterial therapy and cause a severe local or generalized form of intrauterine infection in the fetus and newborn.

The appointment of initial empiric antibacterial therapy for pregnant women with an exacerbation of a chronic genitourinary tract infection is carried out in a hospital and includes catheterization of the genitourinary tract against the background of infusion therapy. Women who underwent drainage therapy during pregnancy by installing a catheter must adjust the use of prescribed antimicrobial drugs taking into account the individual sensitivity of the pathogen, but very often doctors are faced with polyresistant pathogens. Therefore, it is absolutely necessary to establish the pathophysiological influence of pathogens that have different factors of aggression during exacerbation of chronic genitourinary tract infection during pregnancy.

In modern conditions, methodological approaches to animal modeling of various human pathologies are determined by the need to ensure most accurate reproduction of pathological process in experimental conditions, devoid of any adverse reactions that distort the results of experiment. In the variety of experimental models of genitourinary system inflammatory processes, there are several principled methodological approaches.

An ascending urogenital infection modeling with the development of acute pyelonephritis by introducing an inoculum into the urinary bladder through a catheter is recommended by many authors [2, 17]. Modeling of the acute form of pyelonephritis by direct introduction of a bacterial culture into the renal parenchyma, by disrupting the outflow of biological fluid through vessels as a result of their ligation and intravenous introduction of bacterial strains is quite common [6]. The disadvantages of such methods of urogenital infection modelng with the development of an acute form of pyelonephritis through the use of operative access to urinary system organs are the infliction of an operational injury on the animal, which distorts the indicators recorded in the experiment and thereby reduces the purity of obtained data. In addition, with such methods an acute purulent pyelonephritis most often develops, which is atypical for an ordinary clinical situation, especially in fertile women.

With the help of the hematogenous infection method, reference strains that do not have tropism to the uroepithelium are used as an infectious agent, which does not allow to reproduce the typical clinic of ascending chronic pyelonephritis *in vivo*. In addition, histological signs of the inflammatory process are registered in kidneys interstitium and are not detected in the wall of pelvis and calyx.

The main advantages of the proposed methodology for modeling the genitourinary system chronic inflammatory process in WAG population rats are that the method is implemented on animals that have the closest similarity of the histomorphological parameters of the placental barrier to the human body, which

allows extrapolating the results to the human body with sufficient confidence and reproduction of the primary source of the infectious-inflammatory process in the genitourinary tract of mother's body has real compatibility with the problem of intrauterine development of the pathology in offspring's kidneys for humans.

Streptococcus pyogenes and *Proteus mirabilis* enter the organs of the genitourinary tract by the ascending route (a catheter is used), interact with Toll-like receptors, that leads to inflammatory reaction development which is overpowering, and turns to kidney tissue damage with fibrosis development. An important role in development of a chronic genitourinary tract infection in pregnant women is attributed to the reduction of non-specific resistance and the imbalance of the body's immune reaction. It is known that an immunodeficiency state is registered in almost every pregnant woman, which is manifested by a decrease in the number of T-lymphocytes and an increase in B-lymphocytes, suppression of phagocytic activity of leukocytes, nonspecific factors of immune protection, such as complement and lysozyme, and an increase in circulating immune complexes [13, 18].

The mechanism of development of chronic genitourinary tract infection caused by *Proteus mirabilis* and *Streptococcus pyogenes* is justified by the effect of pathogenicity and virulence factors of the causative agent.

Thus, the attachment of *Proteus mirabilis* to the tissues of the macroorganism depends on the activity of its fimbriae, which contain certain compounds that allow it to attach to certain places in the host's body (the endothelium of genitourinary tract) or other surfaces (for example, medical catheters), therefore, the fimbriae of *Proteus mirabilis* contribute to rapid adhesion to the uroepithelium, and flagella cause colonization of the pathogen with subsequent formation of dense biofilms. The main factor in the pathogenicity of *Proteus mirabilis* is lipopolysaccharide, which, together with toxic agglutinin, cause cell aggregation and cytotoxicity on one side, and hemolysin phenomenon on the other side, enhances and prolongs the effect of cytotoxicity. Other virulence enzymes, urease, in particular, hydrolyzes urea as an energy source with the formation of ammonia and carbon, this causes local inflammation with a shift in pH to the alkaline side, leads to edema and stagnation of urine, in addition, alkaline urine reduces the solubility of both organic and inorganic compounds, contributing to precipitation and formation of stones (for example, magnesium ammonium phosphate and calcium apatite carbonate). Proteases disrupt the structure of IgA and IgG and lead to their degradation, increase the permeability of blood vessels and deaminate amino acids, which, together with the action of deaminase, leads to the production of α-ketoacid siderophores and the release of iron. Hyaluronidase contributes to the penetration into the cells of the macroorganism [3, 11, 19].

The pathogenicity factors of *Streptococcus pyogenes* that determine the development of a chronic genitourinary tract infection, are M-protein as the main as protects *Streptococcus pyogenes* from phagocytosis. The second ones are exotoxins, such as leukocidin, which destroys immunocompetent cells, leukocytes, suppresses

their phagocytic activity, and necrotoxin, which causes tissue necrosis in the cite of attachment and reproduction of pathogen. Virulence enzymes such as hyaluronidase, increases the permeability of tissues, which facilitates the penetration and spread of the pathogen throughout the body; DNase increases spreading of the pathogen and reduces the exudate viscosity; protease suppresses the immune response and increases the spread of *Streptococcus pyogenes* throughout the genitourinary tract; streptodornase destroys the tissues of genitourinary tract and contributes to the penetration of pathogen into the bloodstream; streptokinase contributes to fibrin clots destruction and allows bacteria to colonize the body; C5 peptidase destroys the C5a component of complement and allows *Streptococcus pyogenes* to avoid phagocytosis.

Thus, long-term antigenic load in both cases leads to pathophysiological and histomorphological changes in the organs of genitourinary tract, hemodynamic disturbances represented by edema, full blood vessels and small focal hemorrhages and inflammatory polymorphic cellular infiltration: focal in the cortical layer and diffuse in the brain layer with the presence of lymphocytes, macrophages, plasma cells, single neutrophils, eosinophils, which confirm the development of a chronic genitourinary tract infection (fig. 7).

Advantages of the proposed methodology for modeling the genitourinary system chronic inflammatory process allow it to be considered an adequate model of the process of development of intrauterine pathology of the fetus, which also occurs in a pregnant woman. An experimental study of pathogenesis of development of kidneys pathology in offspring under the influence of urogenital tract chronic inflammatory process by the proposed method will allow to determine the directions of correction and prevention of the pathology of pregnancy in order to prevent the birth of sick offspring.

Therefore, the introduction of an infectious-inflammatory agent isolated from pregnant women with a chronic course of the urogenital system into the urogenital tract 20 days before pregnancy leads to the development of a chronic inflammatory process of the genitourinary system.

The development of this model allows to study pathogenetic features of the course of chronic genitourinary tract infection in pregnant women, to verify with high diagnostic accuracy the degree of development of uropathology and obstructive and sclerotic changes in the kidneys. The established pathogenetic features of the development of chronic genitourinary tract infection reveal patterns of intrarenal blood circulation disorders and can be used for objective early assessment of structural and functional changes in the organs of the urinary system, as well as serve as a basis for individual therapy.

The practical significance of the development of this model lies in further research on solving the problems of formation of chronic urogenital pathology for scientists and doctors in determining the leading criteria, such as the degree of thinning of the parenchyma and the cortical layer of the kidneys, and the determination of the endothelial factor. The determination of the maximum systolic velocity at the level of the main renal artery, the end diastolic velocity at the level of parenchymal arteries, the level of vasculo-endothelial factor and other indicators that are markers of the

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formation of chronic renal failure, especially during pregnancy, is of great importance for doctors. The obtained results determine the expediency of including children born from mothers with chronic genitourinary tract infection in the standard of dispensary observation.

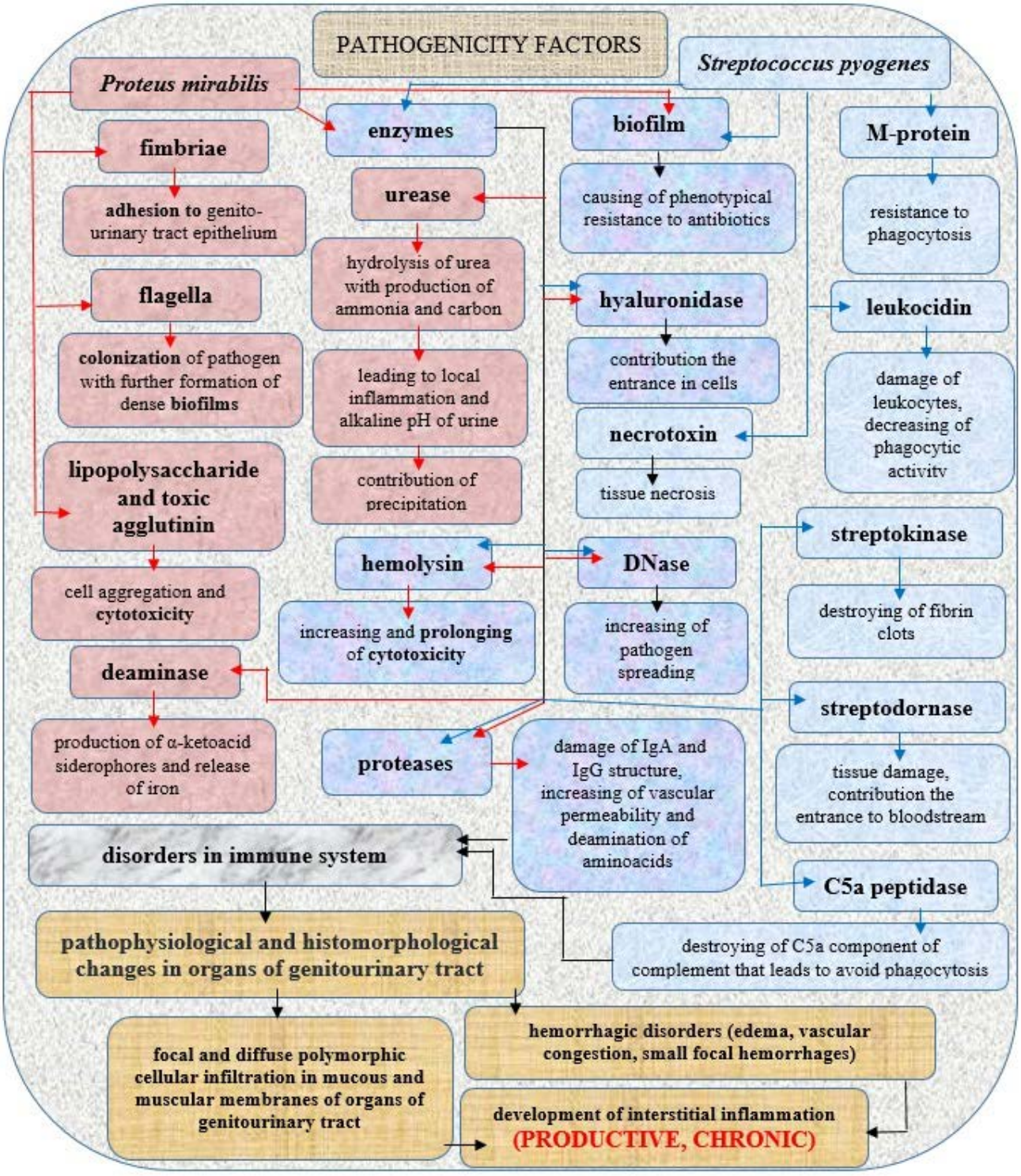

Fig. 7. The mechanism of development of chronic genitourinary tract infection caused by Proteus mirabilis and Streptococcus pyogenes.

Establishing the leading laboratory-instrumental criteria with the help of the developed experimental model as prognostic indicators will contribute to the differentiated selection of patients for invasive methods of in-depth urogenital examination, the choice of tactics for the management of pregnant women, complement the recommendations for dynamic monitoring.

Thus, a comprehensive approach to establishing the leading pathophysiological links in the pathogenesis of the chronic bacterial genitourinary tract infection will contribute to the prevention of the development of renal failure, the reduction of relapses and the effective implementation of preventive measures among pregnant women with this pathology. All this will prevent the development of nephropathology in babies born from mothers with this pathology and reduce the risk of complications, develop algorithms for the examination and treatment of pregnant women, forecasting and prevention of bacterial genitourinary infection, and reduce the risk of disease progression and relapses.

Conclusions.

1. An alternative model of the chronic genitourinary tract inflammatory process was developed and described in an experiment on female rats with the introduction of uroisolates of *Proteus mirabilis* and *Streptococcus pyogenes* directly into the urethra and vagina using a catheter. After 10 days, reference strains were introduced intraperitoneally in order to increase the antigenic load and reduce the activation of the local immune response.
2. To develop the methodology, there were used uroisolates, which most often caused chronic course of genitourinary tract infections in pregnant women, such as *Proteus mirabilis* and *Streptococcus pyogenes*.
3. *Proteus mirabilis* and *Streptococcus pyogenes* uroisolates were selected as pathogens capable of forming dense biofilms, which are the main factor of bacterial pathogenicity.
4. Unlike other methods of experimental modeling of genitourinary system inflammatory process, this method reproduces the prolonged inflammatory process throughout the pregnancy of laboratory animals and more accurately reflects the similar process in pregnant women.
5. This original method of modeling of genitourinary system chronic inflammatory process should be used when studying the development of pathological processes in offspring born from mothers with pathology of urogenital tract.

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