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ASSESSMENT OF THE FACTORS OF INSUFFICIENT EFFECTIVENESS OF TREATMENT OF INFLAMMATORY GENITAL DISEASE CAUSED BY CHLAMYDIA

*The prevalence of the latent course of genital inflammatory disease caused by chlamydia and its untimely diagnosis lead to an increase in the frequency of etiologically unidentified inflammatory processes and the application of unjustified treatment tactics. The **aim** of the research was to identify the causes of insufficient effectiveness of traditional treatment methods for genital inflammatory disease caused by chlamydial infection in women and men. **Methods.** Gynecological, paraclinical, and microbiological examinations were conducted on 170 women aged 19 to 35 years with chronic genital inflammatory disease (with an inflammation duration ranging from 2 to 12 years), which was complicated by infertility in 48 (28.2%) patients. Parallel examinations were conducted on 165 men aged 20 to 42 years with chronic urethritis and/or prostatitis of chlamydial etiology (with a disease duration ranging from 3 to 11 years). In the group of women (24 examined) with chronic genital inflammatory disease of chlamydial etiology, hospitalized for surgical treatment of tubal infertility, microbiological and morphological studies of surgical material fragments were conducted. Additionally, the concentration of doxycycline hydrochloride in the tissues of the fallopian tubes, blood, and urine was determined after oral administration of the drug on the 3rd, 6th, and 9th days. Similarly, in men with chronic urethritis of chlamydial etiology, the concentration of doxycycline hydrochloride in epithelial cells of the urethral mucosa, blood, and urine was determined. **Results.** The study established that the insufficient effectiveness of treatment for chronic genital inflammatory disease caused by chlamydia in both women and men is due to the absence of the necessary minimum inhibitory concentrations of antibacterial drugs (tetracycline group) when administered orally to suppress chlamydia at the site of infection. Additionally, the degree of anatomic and functional changes in the fallopian tubes (their sclerotic destruction due to chlamydial infection) in women and the urethral epithelium in men contribute to the treatment ineffectiveness.*

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Conclusions. *One of the primary factors contributing to the insufficient effectiveness of conservative treatment methods for genital inflammatory disease of chlamydial etiology is the untimely administration of treatment. At this stage, anatomical and functional changes in the pelvic organs become irreversible. Morphological changes in the tissues of the fallopian tubes due to chlamydial infection are characterized by the development of sclerotic destruction of the organ against the backdrop of disrupted intra-organ blood circulation. This explains the insufficient effectiveness of traditional anti-inflammatory treatment regimens for chronic salpingitis of this etiology with tetracycline antibiotics when administered orally in the later stages of the disease.*

Keywords: *genital inflammatory disease, chlamydial infection, factors contributing to insufficient treatment effectiveness.*

Scientific knowledge of the morphology, physiology, and intracellular parasitism of chlamydia has expanded our understanding of the pathogenic mechanisms of chlamydial infection affecting the reproductive organs of women and men (Den Heijer et al., 2019; Huai et al., 2020; Delcroix, 1997). Given the widespread prevalence of chlamydial infections in various locations and the negative medical and social consequences of this infection, there is a need to improve traditional diagnostic methods and interpret the results, which is crucial for the successful treatment of patients with this infection (Petersen, et al., 2021; Romaschenko, 2000).

The prevalence of the latent course of genital inflammatory disease caused by chlamydia and its untimely diagnosis lead to an increase in the frequency of etiologically unidentified inflammatory processes and the application of unjustified treatment tactics (Rudenko et al., 2023; Romashchenko & Yakovenko, 2022). The development of antibiotic-resistant bacterial forms and their transformation into L-forms contribute to the increased frequency of recurrences, complications, and the spread of chlamydial genital inflammatory disease (Paira et al., 2021; Edwards et al., 2019; Witkin et al., 2017).

The **aim** of the research was to identify the factors contributing to the insufficient effectiveness of traditional treatment methods for genital inflammatory disease caused by chlamydial infection in women and men.

Materials and Methods. An examination was conducted on 170 women aged 19 to 35 years with chronic genital inflammatory disease (with

an inflammation duration ranging from 2 to 12 years), which was complicated by infertility in 48 (28.2%) patients. Concurrently, following gender aspects in the comprehensive research program, an examination was conducted on 165 men aged 20 to 42 years with chronic urethritis and/or prostatitis of chlamydial etiology (with a disease duration ranging from 3 to 11 years).

The microbiological examination included detecting bacteria of various taxonomic groups and fungi of the genus *Candida* in samples of pathological material (Barer et al., 2020). Chlamydia detection was performed using chlamydial immunofluorescence reactions (direct immunofluorescence — DIF or indirect immunofluorescence — IIF), polymerase chain reaction (PCR), and cytology of smears. The levels of immunoglobulins specific to the chlamydial antigen in blood serum were determined by the enzyme-linked immunosorbent assay (ELISA) (Schachter et al., 1995). Diagnostic isolation of chlamydia from pathological material was conducted in McCoy and L-929 cell cultures (Paa- vonen et al., 1987).

Histological examination of tissue biopsies from the fallopian tubes, obtained during surgical treatment of 24 women with tubal infertility, was performed after staining the preparations with hematoxylin-eosin, Van Gieson, and Hotchkiss-McManus methods. To determine the concentrations of the antibiotic in blood, urine, epithelial cells of fallopian tube fragments (in women), and urethral mucosa (in men) during the treatment dynamics, a microbiological method was used (De Brux & Palmer, 1979).

Results. A comprehensive clinical and microbiological examination of 170 women with chronic genital inflammatory disease revealed the presence of various pathogens in the cervical canal content in 117 (68.8%) patients. Specifically, *E. coli* was found in 45 (26.5%), *Proteus* sp. — in 42 (24.7%), *Pseudomonas aeruginosa* — in 8 (4.7%), *Citrobacter freundii* — in 9 (5.3%), *Enterobacter* sp. — in 5 (2.9%), *Klebsiella pneumoniae* — in 5 (2.9%), and *Acinetobacter* sp. — in 4 (1.8%), with critical (up to 9×10^4 CFU/mL) and high (at least 1×10^5 CFU/mL) microbial counts. In addition to classical bacteria, mycoplasmas were detected in 29 (17.1%) patients, ureaplasmas — in 15 (8.8%), and chlamydia — in 82 (48.2%).

When conducting a comparative assessment of the informativeness of various methods for etiological diagnosis of genital inflammatory diseases in both women and men, we confirmed the necessity of comprehensive examination using cultural, serological, genetic, and immunofluorescence methods. For detecting chlamydia, the most reliable results were obtained through cultural diagnostics in McCoy and L929 cell cultures, as this method uniquely allows for the assessment of the pathogen's viability.

The polymerase chain reaction (PCR) method is highly sensitive, allowing for the detection of the pathogen even in small quantities. However, caution should be exercised in interpreting the results after etiotropic therapy. Simultaneous immunofluorescence examination allows for not only the detection of chlamydia but also the quantitative assessment of infected cells. Determining the levels and classes of immunoglobulins using ELISA methods allowed for the assessment of the activity and, to some extent, the prevalence of the process. Routine cytological examination of scrapings allowed for the assessment of the general condition of the mucous membrane, with inclusions characteristic of chlamydia found in 30–40% of cases. The simultaneous use of these methods enabled not

only the etiological verification of the diagnosis but also the characterization of the dynamics of the inflammatory process, including chlamydial etiology.

Examination of 165 men with chronic urethritis and/or prostatitis and established etiological diagnosis showed that chlamydia was detected in monoculture in 45 (27.3%) patients, in association with mycoplasmas — in 31 (18.8%), with ureaplasmas — in 20 (12.1%), and with classical bacteria — in 69 (41.8%) cases.

Patients diagnosed with genital chlamydial infection, both men and women, underwent treatment in accordance with the recommendations of the World Health Organization (WHO). The rationale for antibacterial therapy was determined considering the microbial count and possible synergy or antagonism of microorganisms in the case of mixed infection. Treatment also involved simultaneous detection and management of somatic pathology, correction of immunological disorders based on individual characteristics, restoration of normal vaginal microbiota, prevention of recurrence of the disease, examination and treatment (if necessary) of all family members, simultaneous examination and treatment of sexual partners, and clinical, microbiological, and immunological monitoring of treatment effectiveness 1 and 3 months after its completion.

When determining the treatment strategy, the overall condition of the patients, localization of the pathological process, nature of pathological changes in both the pelvic organs and other organs/systems, their interrelation, and the presence of complications due to the inflammatory process of chlamydial etiology were taken into account.

We identified a group of 74 female patients with chronic salpingo-oophoritis of chlamydial etiology, with disease durations ranging from 3 to 12 years. All examined patients exhibited pronounced anatomical changes in the pelvic organs, predominantly characterized by adhe-

sion formation. Additionally, background diseases of the cervix were found in 34 (45.9%) of these patients. Among the examined patients in this group, chlamydia was detected as follows: in monoculture — in 5 (6.7%) patients, in association with ureaplasmas — in 22 (29.8%), with mycoplasmas — in 26 (35.1%), and with classical bacteria — in 21 (28.4%) cases. It is worth noting that serological examination of these women revealed high titers of anti-chlamydial IgG antibodies, ranging from 1:80 to 1:320.

The patients with chronic salpingo-oophoritis caused by chlamydial infection underwent comprehensive anti-inflammatory therapy with the tetracycline group drug doxycycline hydrochloride and the quinolone group drug tarivid, prescribed in accordance with WHO recommendations (Ross et al., 2007). The examined patients were divided into three groups based on the complex treatment regimen. The first group included 20 women who received doxycycline hydrochloride at a dose of 0.2 g on the first day of treatment and 0.1 g for the next 9 days simultaneously with antifungal, desensitizing agents, and hepatoprotectors. The second group comprised 30 patients with chlamydial salpingitis who received similar treatment with tarivid prescribed at a dose of 200 mg twice daily for 10 days. The third group consisted of 24 women with inflammatory pelvic diseases of chlamydial etiology and tubal infertility who were prepared for surgical treatment without antibiotic therapy.

We evaluated the effectiveness of therapy at 1 and 3 months, considering:

- The absence of the inflammatory agent (chlamydia) detected by PIF, PCR, and culture diagnostic methods.
- The resolution of clinical symptoms (pain, genital discharge, hyperemia of vaginal and cervical mucosa, adnexal tenderness, pain on movement, absence of dyspareunia).

Analysis of clinical and laboratory examination results of patients from both groups showed that positive dynamics after the first

course of treatment for inflammatory genital diseases caused by chlamydial infection, when doxycycline hydrochloride was included in the anti-inflammatory therapy regimen, was observed in 20.0% of cases, and with tarivid — in 40.0% of cases.

To determine the factors contributing to the insufficient effectiveness of treatment for inflammatory genital diseases of chlamydial etiology, we measured the concentration of doxycycline hydrochloride directly in the lesions — in the tissues of the fallopian tubes obtained during the surgical treatment of patients in the third group. This group comprised 24 women with inflammatory diseases of the pelvic organs of chlamydial etiology complicated by tubal infertility.

The examined women received doxycycline hydrochloride the day before the surgery according to the standard treatment regimen. However, depending on the duration of the therapy, they were divided into three subgroups: the first subgroup included 6 women operated on the third day from the start of therapy, the second subgroup comprised 8 patients operated on the 6th day, and the third subgroup consisted of 10 women who underwent surgery on the 9th day from the start of antibiotic therapy. The concentration of the antibiotic was determined in tissue fragments of the fallopian tubes obtained during surgical treatment on days 3, 6, and 9 of therapy.

The conducted studies revealed that the concentration of doxycycline hydrochloride in the serum corresponded to the necessary therapeutic level within the range (depending on the time from drug administration) from $0.98 \pm 0.3 \mu\text{g/mL}$ (on the 3rd day) to $1.8 \pm 0.4 \mu\text{g/mL}$ (on the 9th day) (Fig. 1).

When taking doxycycline hydrochloride orally, its concentration in the urine remained consistently within therapeutic levels (ranging from $15.54 \pm 1.2 \mu\text{g/mL}$ to $37.4 \pm 3.1 \mu\text{g/mL}$). Meanwhile, the concentration of the antibiotic in the epithelial cells of the fallopian tube tissues was extremely low, ranging from traces (on the 3rd

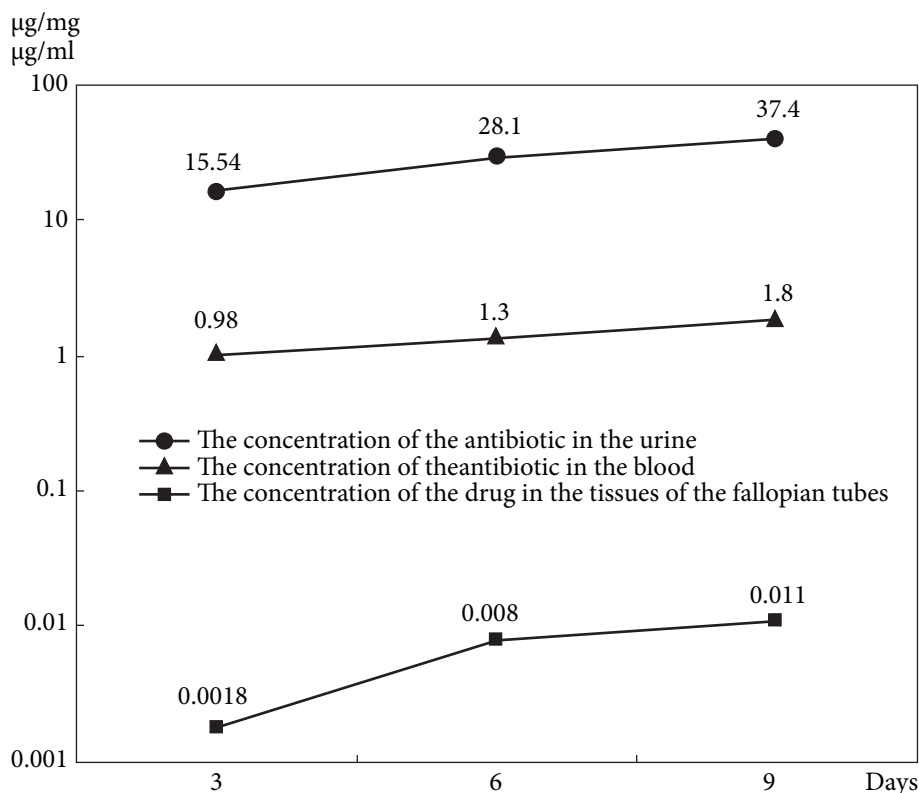


Fig. 1. Concentration of doxycycline hydrochloride in the tissues of the fallopian tubes, in the blood, and in the urine of women

day) to 0.018 µg/mg (on the 9th day) depending on the duration of drug intake, which was significantly below the minimal inhibitory concentrations (MIC) for chlamydia (ranging from 0.5 to 1.4 µg per 1 mL of medium).

Among 24 women hospitalized for surgical treatment of chronic salpingo-oophoritis complicated by tubal infertility, tubo-ovarian inflammatory formations with occlusion of the distal part of the fallopian tubes were detected in 16 cases. It is worth noting that in two women aged 18 and 19 years, hospitalized for surgical treatment with pronounced anatomical changes in the pelvic organs, an early onset of sexual activity (from the age of 16) was in the medical history, accompanied by latent development of the inflammatory process, which reached its peak in a short period of time.

Microbiological examination of samples from the fallopian tubes, obtained directly from the site of infection during surgical treatment, showed that chlamydia were detected in a monoculture in 18 out of 24 operated women. Determination of chlamydia both in the epithelial cells of the cervical canal in these women before surgery and directly in the tissues of the fallopian tubes during surgical intervention confirms the transcanalicular mechanism of spread of this pathogen to the upper parts of the genital tract. The detection of elevated antibody titers (from 1:80 to 1:320) to chlamydial antigen in the blood serum of these patients in the IFA reaction allowed confirming the causative role of *C. trachomatis* in the development of generalized inflammatory process of this etiology.

The final conclusion regarding the degree of pathognomonic activity of chlamydia in the de-

velopment of salpingitis was made taking into account the study of the morphological substrate of the removed fragments of fallopian tubes in the examined women.

During the operation, upon visual observation of the fallopian tubes affected by chlamydia, the latter were dilated in diameter from 2.5 to 3 cm, curved due to peritubal adhesions with pronounced vascular patterns. Flat adhesions in the form of «cuffs» enveloped the ovaries, extending to the walls of the pelvis. In the Douglas space, there was a small amount of turbid fluid. In some patients, isolated pseudobulbar eruptions were visualized on the parietal peritoneum. In all cases, significant anatomical changes in the pelvic organs were combined with the typical «triad of signs», according to J. Henry-Sachet, characteristic of chlamydial infection (Henry-Suchet, 1997), namely i) multiple adhesions with pronounced vascular patterns, which in the form of «cuffs» can wrap around the fallopian tubes and ovaries; ii) pseudobulbar eruptions on the parietal peritoneum, and iii) accumulation of turbid fluid in the Douglas space.

Microscopically, swelling of the fallopian tube wall, mainly due to thickening of the submucosal layer, was noted. Disruption of the histarchitecture of fibrous structures with areas of collagen fiber clustering, which is one of the signs of sclerotic changes, was also observed. At the same time, atrophy of the ciliated epithelium was noted. In the stroma of the fimbriae and in the submucosal layer, small, predominantly perivascular infiltrates were present.

The walls of arterioles and small-caliber arteries were significantly thickened due to hypertrophy of the muscular layer as a result of narrowing of the vessel lumen. Marked disruption of intraorgan blood circulation was established in the submucosal layer, manifested by the appearance of foci of interstitial hemorrhage. Inflammatory infiltration was characterized mainly by an increased content of lymphoid cells.

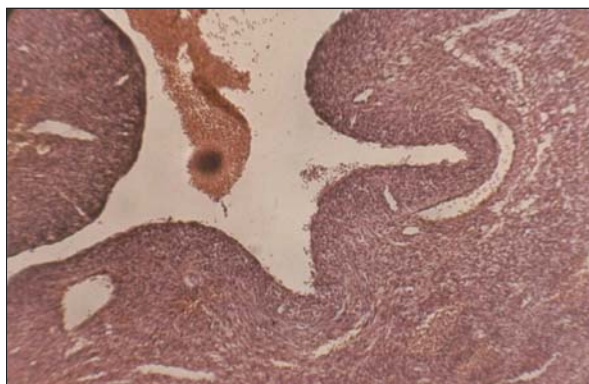


Fig. 2. Patient P., 35 years old. Pronounced sclerosis of the submucosal and mucosal layers of the fallopian tube, smoothness, and the absence of fimbriae in the tube layer — «bald tube phenomenon»

The presented data indicate that women with chronic inflammatory genital diseases of chlamydial etiology, due to the latent development of salpingo-oophoritis, sought medical attention from obstetrician-gynecologists untimely, when anatomofunctional changes in the pelvic organs had reached their peak and were already irreversible. During the morphological study of fallopian tube tissues affected by chlamydial infection, the phenomena of sclerosis of the submucosal and mucosal layers of the tube, fibrotic deformation of the fimbriae, came to the forefront. This created the impression that the inflammatory process had progressed slowly with gradual development of sclerotic changes in the affected organ (Romaschenko, 1989). Fibrotic deformation of the stroma of the fimbriae was accompanied by their smoothing and rigidity, ultimately leading to the formation of the «bald tube phenomenon» (Fig. 2).

Thus, inflammatory genital diseases of chlamydial etiology were accompanied by significant changes in the histoarchitecture of the fallopian tubes and the development of their anatomic and functional inadequacy due to sclerosis. The restoration of their functional activity is associated with significant difficulties, especially when using traditional conservative treatment meth-

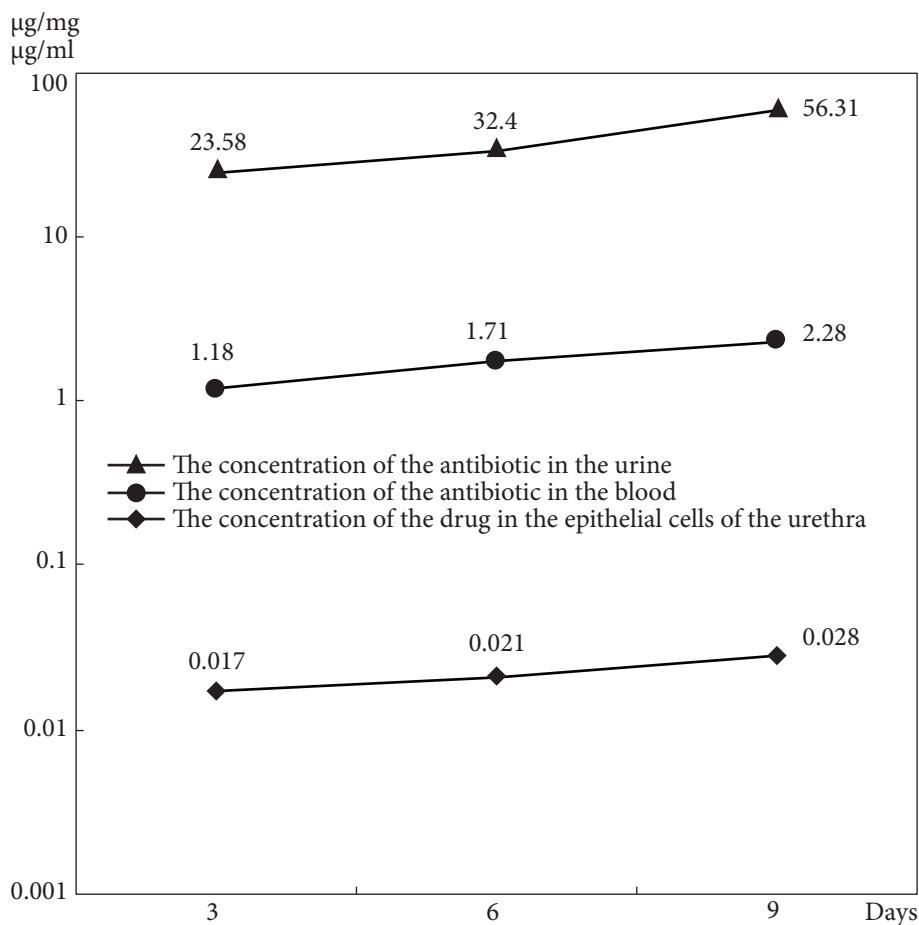


Fig. 3. Concentration of doxycycline hydrochloride in the epithelial cells of the urethra, in the blood, and in the urine in men

ods with antibacterial drugs, the concentrations of which do not yield clinical effects.

In parallel, an analysis of the reasons for the insufficient effectiveness of treatment for chronic urethritis of chlamydial etiology was conducted in 165 men with a disease duration ranging from 3 to 12 years. Considering the obligate intracellular parasitism of chlamydia, we determined the concentration of doxycycline hydrochloride at the focus of infection, in the area directly affected by chlamydia on the urethral mucosa — in the cells of the cylindrical epithelium of the urethra. Simultaneously, to compare the obtained results, concentrations of the antibiotic in blood serum and urine were determined.

The results of the conducted research showed that the concentrations of the antibiotic in the blood serum of the examined men were at therapeutic levels — ranging from 1.18 ± 0.15 µg/mL (on the 3rd day of drug intake) to 2.28 ± 0.71 µg/mL (on the 9th day of doxycycline hydrochloride intake) (Fig. 3).

The concentration of doxycycline hydrochloride in the urine of male patients ranged from 23.58 ± 1.25 to 56.31 ± 3.36 µg/mL. Upon oral administration of doxycycline hydrochloride, the concentrations of the antibiotic in the epithelial cells of the urethral mucosa were extremely low and ranged (depending on the duration of drug intake) from 0.017 µg/mg (on the

3rd day of treatment) to 0.028 µg/mg (on the 9th day), which is significantly below the MIC for chlamydia.

Discussion. The conducted research has demonstrated that one of the factors contributing to the insufficient effectiveness of traditional treatment methods for chronic inflammatory genital diseases with long-term recurrent chlamydial infection in both women and men, using antibiotics (such as doxycycline hydrochloride), is the extremely low concentrations of the drug directly at the sites of infection, that is, in the epithelial cells of the fallopian tubes and the urethral mucosa.

On the other hand, it should be noted that among the examined women and men, inflammatory urogenital diseases of chlamydial etiology, which developed over a period of 2 to 12 years and predominantly had a latent course of the inflammatory process at the time of examination, were accompanied by pronounced changes in the reproductive organs. In women, the inflammatory genital disease caused by chlamydia was characterized by the formation of destructive changes in the fallopian tubes with occlusion of their distal part and the development of pyosalpinx. Numerous adhesions with a network of branching capillaries around the fallopian tubes and ovaries, as a sign of generalized inflammatory process in the pelvic organs under chlamydial infection, indicates the aggressiveness of the disease. Histomorphological examination of fallopian tubes damaged by chlamydia revealed their sclerotic destruction with fragments of fibrotic deformation.

Thus, the conducted research has shown that patients with chlamydial genital infection sought specialized medical help with delay, when changes in the reproductive organs in women and men had reached their peak and were irreversible.

Conclusions. One of the factors contributing to the insufficient effectiveness of conservative treatment methods for inflammatory genital diseases of chlamydial etiology is their untimely

implementation, leading to irreversible structural and functional changes in the pelvic organs.

Morphological changes in the tissues of the fallopian tubes during chlamydial infection are characterized by the development of sclerotic destruction of the organ, accompanied by disturbances in intraorgan blood circulation. This explains the inadequate effectiveness of traditional anti-inflammatory treatment regimens for chronic salpingitis of this etiology using tetracycline antibiotics administered per os.

Furthermore, the low effectiveness of treating inflammatory genital diseases of chlamydial etiology using traditional methodological approaches, both in women and men, exemplified by the use of doxycycline hydrochloride, is explained by the failure to achieve necessary therapeutic concentrations of the antibiotic at the sites of infection, particularly in the epithelial cells of the fallopian tubes and urethra. These concentrations are tens of times lower than the minimum inhibitory concentration (MIC) for chlamydia. Considering that chlamydia is susceptible to antibiotic therapy at the stage of reticulate bodies (RB), and oral administration of drugs results in their low concentrations at the sites of infection due to sclerosis development, the inadequate effectiveness of treating patients with urogenital chlamydia using traditional therapeutic methods becomes evident.

The presented data logically necessitate the creation of an organizational system for early screening of patients suffering from inflammatory diseases of the reproductive organs. After establishing the degree of infection and the types of sexually transmitted pathogens, appropriate treatment should be prescribed. Etiologically justified therapy should preferably be carried out through intravenous administration of antibacterial agents with anti-chlamydial action along with immunomodulatory therapy, drugs improving blood rheological properties, and local treatment. Additionally, individual characteristics of micro- and macroorganisms interaction,

as well as the degree of anatomical and functional changes in the reproductive organs, should be taken into account in each specific case.

Conducting research and scientific developments to optimize the treatment methods for

genital chlamydial infections in women and men to prevent disease recurrence is one of the current challenges of modern medical science.

Conflict of Interest. The authors declare that they have no conflict of interest.

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ОЦІНКА ЧИННИКІВ НЕДОСТАТНЬОЇ ЕФЕКТИВНОСТІ ЛІКУВАННЯ ЗАПАЛЬНОЇ ХВОРОБИ ГЕНІТАЛІЙ, СПРИЧИНЕНОЇ ХЛАМІДІЯМИ

Переважаючі латентного перебігу запальної хвороби геніталій, спричиненою хламідіями та її несвоєчасна діагностика призводять до збільшення частоти випадків етіологічно нерозшифрованого запального процесу і застосування необґрунтованої тактики лікування. **Мета.** Встановити причини недостатньої ефективності традиційних методів лікування запальної хвороби геніталій, спричиненою хламідійною інфекцією у жінок і чоловіків. **Методи.** Проведено гінекологічне, параклінічне, мікробіологічне обстеження 170 жінок у віці від 19 до 35 років із хронічною запальною хворобою геніталій (з тривалістю запального процесу від 2 до 12 років), що ускладнилося у 48 (28,2%) хворих безпліддям. Паралельно проводилося обстеження 165 чоловіків віком від 20 до 42 років із хронічним уретритом та/або простатитом хламідійної етіології (з давністю захворювання від 3 до 11 років). У групі жінок (24 обстежено) із хронічною запальною хворобою геніталій хламідійної етіології, госпіталізованих на хірургічне лікування з приводу трубного безпліддя, проводилось мікробіологічне та морфологічне дослідження фрагментів операційного матеріалу та визначалась концентрація доксицикліну гідрохлориду в тканинах маткових труб, крові та сечі після прийому даного препарату per os на 3, 6, 9 добу. Аналогічно, у чоловіків з хронічним уретритом хламідійної етіології визначали концентрацію доксицикліну гідрохлориду в епітеліальних клітинах слизової уретри, в крові та в сечі. **Результати.** Встановлено, що недостатня ефективність лікування хронічної запальної хвороби геніталій у жінок та чоловіків, спричиненої хламідіями, пов'язана з відсутністю необхідних мінімальних інгібуючих концентрацій антибактеріальних препаратів (тетрациклінової групи) при їх призначенні per os для пригнічення хламідій у вогнищі ушкодження та ступенем морфофункціональних змін з боку маткових труб (їх склеротична диструкція при хламідійному ураженні) у жінок та епітелію уретри — у чоловіків. **Висновки.** Одним із основних чинників недостатньої ефективності консервативних методів лікування запальної хвороби геніталій хламідійної етіології є його невчасне проведення, коли анатомо-функціональні зміни з боку органів малого тазу стають незворотними. Морфологічні зміни в тканинах маткових труб при хламідійній інфекції характеризуються розвитком склеротичної деструкції органу на тлі порушення внутрішньоорганного кровообігу, що пояснює недостатню ефективність традиційних схем протизапального лікування хронічних сальпінгітів даної етіології антибіотиками тетрациклінового ряду за їхнього призначення per os на пізніх етапах розвитку захворювання.

Ключові слова: запальна хвороба геніталій, хламідійна інфекція, чинники недостатньої ефективності лікування.