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ASSESSMENT OF RISK FACTORS OF SEPTIC COMPLICATIONS OF THE PUERPERIUM

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Abstract

Postpartum purulent-septic complications (PPSC) and their problems are most urgent for modern obstetrics due to their significant frequency. Maternal sepsis is one of the leading causes of maternal mortality around the world, accounting for about one-tenth of the global number of maternal deaths. Understanding the risk factors for the development of septic complications of puerperium is important for preventive strategies.

Aim. To study the possibility of forming high-risk groups on the basis of analysis of anamnestic data and the course of puerperium in women with PPSC as part of the preventive measures for the development of such complications.

Materials and methods. The first stage of the study involves a retrospective analysis for the allocation of risk factors for the development of PPSC in women, who underwent inpatient treatment for this pathology - main group (n=108); control group (n=35) – parous with uncomplicated flow of the postpartum period. Prospective research enrolled 65 pregnant women with extragenital pathology and/or complicated pregnancy (group 1); 30 pregnant women without severe concomitant somatic pathology with physiological course of pregnancy (group 2). The following were taken into account: age, obstetrical and gynecological history, extragenital pathology, laboratory diagnostic data. Differences in mean values were considered significant with a probability level of at least 95 % ($p<0.05$).

Results. To the risk factors for the development of PPSC, we classified as follows: gynecological diseases in history: menstrual dysfunction, chronic inflammatory diseases of the genital organs, bacterial vaginosis; complications of pregnancy and labor:

preeclampsia, preterm labor, premature rupture of membranes, long anhydrous span, chorioamnionitis, weakness of labor, genital tract ruptures, placental attachment pathology, operative vaginal birth, bleeding; concomitant extragenital pathology: diabetes, obesity, diseases of the urinary system, diseases of the cardiovascular system, respiratory diseases, varicose disease, anemia.

Conclusions. The connection between the presence of concomitant somatic pathology, the complicated course of pregnancy and labor and the subsequent development of septic complications in the postpartum period have been established. Prediction of the risk of their occurrence at the stage of pregraviditic preparation, with various complications of pregnancy and childbirth, especially in women with extragenital pathology, differential prevention will reduce the frequency of PPSC.

Keywords: postpartum purulent-septic complications, risk factors, prevention, vitamin D.

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1. Introduction

Bacterial infections during childbirth and in puerperium are among the leading causes of maternal mortality worldwide, accounting for about 10.7 % of all maternal deaths [1, 2]. Most of the estimated 75000 maternal deaths worldwide occur every year as a result of infections are recorded in low-income countries, while in high-income countries 0.1–0.6 per 1000 births [3, 4]. WHO estimates the global incidence of puerperal infections at 4.4 % among live births, representing more than 5.7 million cases per year [4].

Several factors influence the development of the septic process: the presence of the pathogen (its amount, virulence, associativity), the state of the primary infection and the immune homeostasis (changes in which cause increased sensitivity to infection and create preconditions for activation of the microflora).

The degree of colonization by the microorganisms of the vagina and the cervical canal plays an important role – massive insemination contributes to the development of the infectious process. Especially high risk of ascending infection in pregnant women with concomitant extragenital pathology [5, 6]. Changing the microflora of the vagina during pregnancy can lead to the penetration of microorganisms into the amniotic fluid, increasing the risk of developing complications such as chorioamnionitis, premature rupture of membranes (PROM), preterm labor, increasing the risk of damage of the soft tissues of the genital tract and injuries of the perineum in labor, as well as postpartum endometritis and subinvolution of uterus as a veiled form, which ultimately can lead to the generalization of the process and the development of sepsis [1, 7].

The postpartum period is the most dangerous in terms of the development of infectious complications, due to certain features: the change in the anatomical and functional state of the genital organs and other systems of the body during pregnancy and childbirth; a change in the nature and virulence of microorganisms at the background of reduced immunological status that accompanies pregnancy [1, 5].

In the course of physiological pregnancy, non-specific T-cell suppression (decrease in the absolute number of T-lymphocytes, increase in the absolute and relative number of T-suppressors, decrease in any degree of T-helper cells) is formed, which provides the immunological tolerance of the body of the pregnant woman to the fetus [1]; B-cell immunity is maintained at the normal level, including the concentration of serum Ig in the blood (compensatory response to the exclusion of T-cells from anti-infective protection) [8]. Most authors confirm that a normal pregnancy is accompanied by a transient partial immunodeficiency. Presence of genital and extragenital pathology deepens the state of immunosuppression [1].

Particularly relevant is the study of vitamin D role in the formation of immune status during pregnancy, accounting the high prevalence of vitamin D deficiency in pregnant women (18–84 %) [9]. As shown in many studies, vitamin D has a regulatory role on innateand adaptive immune responses [10]. Vitamin D is known as an immunomodulator, targeting different immune cells, including monocytes, dendritic cells, as well as T-lymphocytes and B-lymphocytes [11]. Vitamin D promotes antimicrobial responses by producing antibacterial peptides and stimulating autophagic activity in macrophages [10]. Several epidemiological studies link inadequate levels of vitamin D with immune status in chronic infections, autoimmune diseases, type 1 diabetes, systemic lupus erythematosus and rheumatoid arthritis [11, 12]. Vitamin D3 deficiency during pregnancy is associat-

ed with an increased risk of infectious complications of pregnancy, including premature birth [13], development of gestational diabetes mellitus, preeclampsia and maternal bacterial vaginosis [9, 14].

Understanding the risk factors for the development of PPSC is important for preventive strategies. This explains the urgency of further studying the problem and finding effective prevention technologies.

2. Aim of research

To study the possibility of forming high-risk groups on the basis of analysis of anamnestic data and the course of puerperium in women with PPSC as part of the prevention measures for the development of such complications.

3. Materials and methods

The first stage of the study involves a retrospective analysis for the allocation of risk factors for the development of purulent-septic complications in women, who underwent inpatient treatment for this pathology of the postpartum period in Lviv Regional Clinical Hospital and Lviv Municipal Clinical First Aid Hospital in 2013–2016 – main group (n=108). Control group (n=35) – parous with an uncomplicated flow of the postpartum period.

At the prospective study, 2 groups of pregnant women were formed, depending on the presence/absence of the following risk factors on the first stage: group 1 (n=65) – pregnant women with extragenital pathology and/or complicated pregnancy; group 2 (n=30) – pregnant women without severe concomitant somatic pathology with physiological course of pregnancy. The following data were taken into account: age, obstetrical and gynecological history, extragenital pathology, laboratory diagnostics data. Concentrations of Ig M, Ig A, Ig G were determined in peripheral blood during the last trimester of pregnancy and after delivery by immuno-enzymatic method using the firms «Vector Best» (Russia) in accordance with the instructions of the manufacturer. Level 25(OH)D3 was measured in the peripheral blood during the last trimester of pregnancy by an immunochemical method with electrochemiluminescent detection (ECLIA) on the Cobas 6000 analyzer (Roche Diagnostics test-system, Switzerland).

Statistical processing of the study results was conducted using the Student's t-criterion. Differences in mean values were considered significant with a probability level of at least 95 % ($p<0.05$).

4. Results

At the first stage of this research, a retrospective analysis of archival medical records was carried out on 108 women (main group) with PPSC, of which 67.59 % (n=73) of women with PPSC, who had vaginal delivery, 32.41 % (n=35) of women with PPSC, who had caesarean section. In control group: 68.57 % (n=24) of women had vaginal delivery; 31.43 % (n=11) of women had caesarean section. Both clinical groups were homogeneous according to age, place of residence, socio-economic status.

The average age of parous from control group was 27.66±0.73 years, main group – 27.05± ±0.46 years. It was found the prevalence of women of early and active reproductive age (18–30 years) in both groups: main group – 75.93 %, control group – 68.57 %.

In both groups, more than half women had 2 and more pregnancies – 62.96 % (main group) and 57.14 % (control group). It was found that in women with PPSC this pregnancy ended up preterm labor, that was significantly higher (12.96 %) in comparison to the control group ($p<0.05$).

In 88.89 % of patients with complicated postpartum period and in 97.14 % of women in control group menarche age has reached at the age range of 11-14 years, while in main group the number of women with late menarche was 4 times higher than in control group. The disorders of menstrual function were 6 times more common in women of main group (54.63 %) compared to the control group (8.57 %) ($p<0.001$).

The analysis of the transferred gynecological diseases has shown a significant frequency of inflammatory diseases of genital organs (21.30 %), bacterial vaginosis and colpitis (57.41 %) in history of the main group, against 2.86 % and 8.57 % respectively in the control group ($p<0,05$). Pa-

thology of the cervix in history of women with PPSC met significantly more (22.22 %) compared to the control group (8.57 %) ($p<0.05$). In addition, infertility and polycystic ovary syndrome (PCOS), were registered only among women from the main group (3.70 %).

Table 1
Peculiarities of gynecological history of women with PPSC in comparison to the control group

Indicator	Main group (n=108)	Control group (n=35)
Menarche (late), %	11.11*	2.86
Menstrual function disturbances, %:	54.63*	8.57
Chronic inflammatory diseases of the appendages and uterus, %	21.30*	2.86
Bacterial vaginosis, colpitis, %	57.41*	8.57
Benign tumors of the uterus and appendages, %	9.26	2.86
Pathology of the cervix, %	22.22*	8.57
Infertility, PCOS, %	3.70	–

*Note: * – p<0.05 between main group and control group*

It should be noted, that 29.63 % of women with PPSC had complicated pregnancy with a threat of interruption at different terms, 14.81 % had preeclampsia, which is significantly higher than in women with uncomplicated course of postpartum period ($p<0.05$). PROM, long anhydrous span, chorioamnionitis were noticed in 13.89 % of women from the main group, while in control group such complications were not met at all. Level of birth canal trauma (vagina and perineal rupture, perineo-, episiotomy) in main group was three times higher than in control group ($p<0.05$). Clinically narrow pelvis (3.70 %) was diagnosed in labor only in women of the main group; labor complicated by the weakness of labor activity (8.33 %), overlapping forceps and symphysis rupture (3.70 %), bleeding and the development of hemorrhagic shock (12.96 %). Placental attachment pathology, manual removal of placenta was observed in 6.48 % of women only in main group. Instrumental examinationof the uterine cavity walls during labor was performed in 14.81 % of women from the main group, which is almost 5 times higher than in control group ($p<0.05$).

Table 2
Peculiarities of the course of this pregnancy and delivery in patients with PPSC in comparison to the control group

Indicator	Main group (n=108)	Control group (n=35)
Threat of abortion/preterm birth, %	29.63	11.43
Preeclampsia, %	14.81	2.86
PRM, long anhydrous span, chorioamnionitis, %	13.89	–
Ruptures, perineotomy, perineorrhaphy %	24.07*	8.57
Symphysis rupture, forceps, %	3.70	–
Defect of the placenta, instrumental examination of the uterine cavitywalls, %	14.81*	2.86
Placental attachmentpathology, manual placental separation and removal, %	6.48	–
Clinically narrow pelvis, %	3.70	–
Weakness of labor activity, %	8.33	–
Bleeding, hemorrhagic shock, %	12.96	–

*Note: * – p<0.05 between the main group and the control group*

Concomitant extragenital pathology in women with PPSC was found in 2–9 times more than in parous with uncomplicated flow of the postpartum period: diseases of the urinary system – nine, diseases of the cardiovascular system and respiratory diseases – in five, diabetes and obesity – twice, anemia – three times higher than in the control group ($p<0.05$). Varicose disease is diagnosed only in women with PPSC (8.33 %). The considerable frequency of the thyroid pathology attracts attention not only in the main group (19.44 %), but also in the control group (17.14 %). In both groups, the percentage of childhood infectious diseases and acute respiratory infections in history was significant.

Table 3

Peculiarities of somatic anamnesis and extragenital pathology in patients with PPSC and the control group

Indicator	Main group (n=108)	Control group (n=35)
Childhood infectious diseases, acute respiratory infections, %	87.96*	60.00
Diseases of the respiratory organs, %	13.89*	2.86
Gastrointestinal diseases, %	12.04	5.71
Cardiovascular diseases, %	13.89*	2.86
Varicose disease, %	8.33	–
Diseases of the urinary system, %	26.85*	2.86
Thyroid diseases, %	19.44	17.14
Diabetes mellitus, obesity, %	26.85*	11.43
Anemia, %	79.63*	25.71

*Note: * – $p<0.05$ between the main group and the control group*

According to our analysis, it was found that complaints from women with PPSC appeared on the 11.19±0.78 day of the postpartum period, but hospitalization into the gynecological department was only on the 14.07±0.89 day. The duration of inpatient treatment in the obstetrical department before delivery in the main group was 8.18±2.25 days (max=22 days), which is approximately 4 times higher than in the control group. It should also be noted, that inpatient treatment in the gynecological department because of PPSC was 11.38±0.62 days (max=63 days). The average duration of antibiotical therapy in main group was 10.4±0.4 days (max=39 days).

It should be noted, that 89.81 % of patients with PPSC had extragenital pathology and/or complications during pregnancy and childbirth (subgroup A), while the proportion of parous without extragenital diseases, uncomplicated pregnancy and labor (subgroup B) in the main group was only 10.19 %. The average duration of inpatient treatment in subgroup A (12.10±0.81 days) exceeded such in subgroup B (8.09±0.76 days) ($p<0.001$). A similar trend was observed regarding the duration of antibiotic therapy: 11.36±0,76 days (subgroup A) versus 7.18±1.19 days (subgroup B) ($p<0.05$). A gynecological hospital admission status of patients subgroup B was rated as satisfactory or moderate. The diagnosis: «peritonitis», «sepsis,» «septic shock» have been exposed to women only from subgroup A. Also in this subgroup were held hysterectomy, blood transfusion, were appointed imipenem group antibiotics. Analyzing the data of bacteriological studies discharge from the uterus, we noted that in women from subgroup A pathogens were represented in associations, while in subgroup B mainly monoinfection was found.

Summing up the findings, we hypothesized that there is a definite link between the presence of concomitant extragenital pathology, complicated pregnancy and childbirth, and the subsequent development of PPSC.

Based on the above analysis, in the second stage prospectively we examined the state of immunity in pregnant women with extragenital pathology and complicated pregnancy (group 1) compared to pregnant women without severe extragenital pathology and uncomplicated pregnancy (group 2). Both groups were homogeneous according to age, place of residence, socio-economic status, term of gestation.

Table 4
Structure of diagnoses in patients with PPSC

Diagnosis	ICD-10 code	Main group (n=108)
– Endometritis, %		29.63
– peritonitis, %	O85	5.56
– sepsis, septic shock, %		7.41
Infection of a surgical wound, %	O86.0	12.96
Thrombophlebitis, phlebothrombosis, %	O87.0–O87.1	12.96
Thromboembolism of the pulmonary artery, %	O88.3	1.85
Thrombosis of cerebral veins in the postpartum period, %	O87.3	4.63
Mastitis, %	O91.1	1.85
Apyous mastitis associated with childbirth, %	O91.2	13.89
Acute adnexitis, %	O86.1	1.85
Other complications of the postpartum period:		
– subinvolution of uterus, %		25.93
– lochiometra, %		50.93
– placental polyp, %	O90.8	7.41
– symphysitis, %		1.85
– pseudomembranous colitis, %		1.85
– postpartum hemorrhage, %		14.81

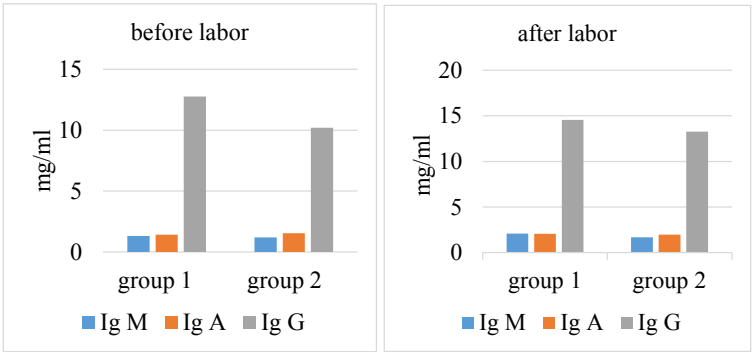
Table 5
Structure of extragenital pathology in group 1 and group2

Indicator	Group 1 (n=65)	Group 2(n=30)
Diseases of the respiratory organs, %	9.23	–
Gastrointestinal diseases, %	10.77	3.33
Cardiovascular diseases, %	23.08*	3.33
Varicose disease, %	12.31	–
Thrombophlebitis, hemorrhoids, %	9.23	–
Diseases of the urinary system, %	21.54*	3.33
Thyroid diseases, %	58.46*	23.33
Diabetes, %	7.69	–
Blood diseases, %	7.69	–
Anemia, %	41.54*	20.00

Note: – $p<0.05$ between group 1 and group 2*

A decrease of Ig A and an increase of Ig G and Ig M in serum before delivery in group 1 was observed in comparison to group 2. There was a faster growth in the postpartum period of Ig M and Ig A levels in group 1 (in 1.6 and 1.5 times respectively), compared with group 2 (1.4 and 1.3 times respectively), and more slowed Ig G growth in group 1 compared to group 2. The results indicated

a difference in the immune response in pregnant women with extragenital pathology and somatic healthy pregnant women with a physiological course of pregnancy.



a *b*

Fig. 1. Indicators of humoral immunity in group 1 and group 2: *a* – before labor; *b* – after labor

The D-status was evaluated in accordance to the recommendations: normal level – 30 –50 ng/ml, suboptimal level – 20–30 ng/ml, moderate deficiency – 10–20 ng/ml, severe deficiency <10 ng/ml. Vitamin D deficiency was determined by the level of 25(OH)D3 in blood serum.

Table 6

The level of vitamin D in blood serum

Vitamin D concentration	group 1 (n=65)	group 2 (n=30)
<10 ng/ml (severe deficiency), %	32.31	13.33*
10–20 ng/ml (moderate deficiency), %	46.15	30.00
20–30 ng/ml (suboptimal level), %	21.54	43.33*
>30 ng/ml (normal level), %	–	13.33

Note: – p<0.05 between group 1 and group 2*

The results of vitamin D3 levels in blood serum of women from group 1 showed a change in comparison to women from group 2 towards a more severe deficiency of vitamin D. The proportion of women with severe vitamin D3 deficiency in group 1 (32.31 %) was in 2.4 times higher than in group 2 (13.33 %) ($p<0.05$). While the number of women with suboptimal level of vitamin D3 in group 2 twice exceeded this indicator in group 1 (43.33 % and 21.54 % respectively) ($p<0.05$).

5. Discussion

Under current conditions PPSC are characterized by changes in etiology, often atypical clinical symptoms and course, which leads to delayed diagnosis and inadequate treatment [1, 15]. The key role in the pathogenesis of PPSC plays «risk factor» [2, 4].

Among the risk factors for the development of PPSC are menstrual function disorders, inflammatory diseases of the genitals, a significant frequency of bacterial vaginosis and colpitis in history of the main clinical group compared to the control group ($p<0.05$). Similar results were presented in the works of other authors [1, 7].

We found that in women with PPSC this pregnancy was complicated by the threat of interruption on different terms and preeclampsia, which is significantly higher than in the group of women with uncomplicated flow of the postpartum period ($p<0.05$). Other authors also noted a strong association between preeclampsia/eclampsia and septic processes in the postpartum period [16, 15]. This pregnancy was significantly more likely to be completed with preterm labor in women with PPSC compared to women from the control group ($p<0.05$), which is confirmed in other studies [16, 17].

Clinically narrow pelvis was diagnosed in labor only in women with PPSC; the delivery was complicated by the weakness of labor, symphysis rupture and forceps, bleeding and the development of hemorrhagic shock. Postpartum haemorrhages were associated with progression to severe sepsis and defined as risk factors for severe sepsis in studies by other authors [15, 16].

Long anhydrous span, chorioamnionitis, placental attachment pathology, manual placental separation and removal were observed only in women with PPSC. Indicator of instrumental examinations of the uterine cavity walls in deliveries in the main group was almost 5 times higher than such in the control group ($p<0.05$). These factors were also highlighted by other researchers [5, 6].

Level of birth canal trauma in the group of women with PPSC was three times higher than that in the control group ($p<0.05$). These complications are also highlighted in other studies as a possible risk factor for the development of PPSC [4, 7].

We found that the concomitant extragenital pathology (diabetes, obesity, diseases of the urinary system, cardiovascular diseases, respiratory diseases, anemia) in women with PPSC was found much more frequent than in parous with uncomplicated postpartum period ($p<0.05$). Acosta C. D. et al. [15] identified diabetes as a risk factor for sepsis, and in women with diabetes the risk of severe sepsis was 47 % higher. In a number of studies, chronic hypertension is defined as a risk factor for severe sepsis [1, 15]. The associations between maternal sepsis and cardiovascular diseases are found in Al-Ostad et al. [16] study. Bamfo J. [6] noted that obese women have 3.5 times higher risk of infection compared with women of an ideal body mass index. Anemia, as a risk factor for the development of PPSC, is highlighted by other authors [5, 17].

Analyzing all the data, we found that significantly more ($p<0.05$) women with PPSC had concomitant extragenital pathology and/or complicated pregnancy and labor. A gynecological hospital admission status of such patients was rated as severe or moderate. The average length of inpatient treatment stay in such cases was significantly higher in the parous with extragenital pathology ($p<0.001$). A similar trend was observed regarding the duration of antibiotical therapy ($p<0.05$).

The postpartum period is very dangerous because of the development of infectious complications, which is due to a decrease in the immunological status, which accompanies the pregnancy. We have identified the differences in the indicators of humoral immunity in pregnant women with concomitant extragenital pathology and/or complicated pregnancy and in pregnant women without severe extragenital pathology. Increasing the levels of Ig M, Ig A, Ig G in healthy women testifies to the natural mechanisms of humoral protection of a woman's body in the postpartum period from a possible infection, and in the absence of risk factors these mechanisms are sufficient.

The role of vitamin D is due to his involvement in the immune system response to bacterial invasion [18]. Flynn L. et al. [19] have found that in patients with vitamin D levels <20 ng/ml, the incidence of infection rates was generally higher, the frequency of septic complications increased. Vitamin D levels <20 ng/ml have a significant impact on the duration of treatment, increasing it [19, 20].

Our studies have shown, that in group 1 various degrees of vitamin D deficiency were found in all women, in group 2 – 13,33 % had a sufficient level of vitamin D. Women with vitamin D deficiency were twice more in group 1 versus group 2 (78 % and 43 % respectively). The proportion of women with severe deficiency of vitamin D in group 1 is higher than twice that in group 2. We have found a more marked deficiency of vitamin D in pregnant women with extragenital pathology and complicated pregnancy.

6. Conclusions

1. The connection between the presence of somatic pathology, the complicated pregnancy and labor and the subsequent development of PPSC have been established.

2. The risk factors for the development of PPSC include:

– gynecological diseases in history: menstrual function disorders, chronic inflammatory diseases of the genital organs, bacterial vaginosis;

– complications of pregnancy and labor: preterm labor, preeclampsia, long anhydrous span, chorioamnionitis, weakness of labor, genital tract ruptures, placental attachment pathology, operative vaginal birth, bleeding;

– concomitant extragenital pathology: diabetes, obesity, diseases of the urinary system, diseases of the cardiovascular system, respiratory diseases, varicose disease, anemia.

3. The prospect of decreasing the frequency of PPSC is to predict and adequately assess the risk of their occurrence at the stage of pregraviditic preparation, with various complications of pregnancy and labor, especially in women with extragenital pathology.

4. Conducting differentiated stage-by-stage prevention will reduce the frequency of PPSC.

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EVALUATION OF THE THERAPEUTIC AND PREVENTIVE POTENTIAL OF THE MEDICINAL PRODUCT CANEPHRON N IN THE TREATMENT OF GESTATIONAL PYELONEPHRITIS IN PREGNANT WOMEN

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Abstract

Background: Gestational pyelonephritis (GP) is one of the most common and serious diseases of the middle and second half of pregnancy, which complicates approximately 6 % of pregnancies, and is one of the leading causes of non-obstetric pre-delivery hospitalization.

Methods. The paper provides data from the open, multicentre, prospective, comparative (parallel group) study in 60 pregnant women diagnosed with gestational pyelonephritis, which were divided into two groups 30 subjects each. Patients in the treatment group received antibacterial therapy for 7 days + treatment with standard dosage of medicinal product Canephron N for 3 months. Patients in the control group received antibiotic therapy alone for 7 days.

Results. The average age of pregnant women at the time of diagnosing was 23±6.23 years; it was the first pregnancy for 39 women (65 %). The most common complaints at admission to the in-patient department were as follows: lumbar pain (96.2 %), dysuria (70.2 %), rise in temperature above 38°C (64.4 %). Leukocyturia and bacteriuria were detected in 100 % of cases with prevalence of E. coli in 84.2 % (101 of 120) of cases. By 30 day in GP patients in the treatment group bacteriuria was detected in 2/30 (6.67 %) patients, and in the control group – in 5/30 (16.7 %) patients (p 1: 2 <0.05), by 60 day in the treatment group – 2/30 (6.67 %), in the control group – 8/30 (26.7 %) (p 1: 2 <0.05), respectively, by 90 day – 3/30 (10 %) and 10 (33.3 %), respectively (p 1: 2 <0.05). The disease relapsed in 1 of 30 (3.33 %) GP patients in the treatment group and 3/30 (10 %) patients in the control group (p 1: 2 <0.05) and 3/30 (10 %) patients in the treatment group with CP, and 7/30 (23.3 %) patients in the control group during the follow-up period (p 1: 2 <0.05).