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# Impact of infectious factors in cervical and vaginal secretions and inflammatory parameters in pregnant women on preterm birth

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**ABSTRACT**

**Introduction**: Preterm birth is a significant clinical issue in obstetrics. According to the World Health Organization's definition, it is characterized by the birth of a newborn after the twenty-second week but before the thirty-seventh week of pregnancy. Prematurity is associated with a significant increase in neonatal and infant mortality and morbidity, as well as long-term negative effects on physical and intellectual development. The direct causes of preterm birth include spontaneous preterm labor (sPTL), preterm premature rupture of membranes (PPROM), and medically indicated preterm termination of pregnancy. Inflammation within the reproductive system is considered the main cause of prematurity, accounting for 25–40% of preterm births. Intrauterine infection-related inflammation triggers the body's inflammatory response, leading to preterm labor and the progressive dilation of the cervix.

The aim of the study was to assess the impact of genital tract infections and elevated C-reactive protein (CRP) levels and leukocyte counts in pregnant women on the occurrence of preterm labor and preterm rupture of membranes leading to preterm birth.

**Materials and methods**: The study was retrospective and included 206 pregnant women, divided into 2 groups: study and control group. The study group consisted of 133 women diagnosed with preterm birth, while the control group included 73 women who delivered at term. Statistical evaluation results were provided for the entire study group, and later stage s involved dividing the group into subgroups of patients with preterm birth due to sPTL and PPROM.

**Results**: The most common pathogens found in the genital tracts of patients in the study group were Gram+ bacteria, which accounted for approx. 50.0% of infections. The second most common pathogens were mycoplasmas (22.56%), followed by Gram– bacteria (19.55%). In the subgroup of patients with preterm birth due to sPTL, Gram+ bacteria were identified in 53.85% of cases. In the subgroup of pregnant women diagnosed with preterm birth due to PPROM, Gram+ bacteria were cultured in 46.91% of swabs. Based on the obtained results of blood morphology with an automatic differential, it was found that the median white blood cells (WBC) values in patients with preterm birth due to sPTL were: at admission, 12.85 thousand/μL; on the day of the swab, 12.9 thousand/μL; and on the first day postpartum, 15.4 thousand/μL. Similar results were obtained in patients with preterm birth due to PPROM, where WBC values were: at admission, 12 thousand/μL; on the day of the swab, 12.9 thousand/μL; and on the first day postpartum, 15.55 thousand/μL. Analyzing CRP concentrations between the subgroups of the study group, it was shown that CRP levels on the day of admission ($p = 0.004$) and on the day of the swab ($p = 0.042$) were significantly higher in the sPTL group, at 6.15 mg/L and 6.3 mg/L, respectively, compared to the PPROM group, where CRP levels were 3.9 mg/L and 4 mg/L, respectively.

**Conclusions**: 1. Acute-phase protein concentrations in serial measurements can be a very useful parameter for assessing inflammation and excluding infections within the genital tract in pregnant women. Additionally, fluctuating CRP levels coincide with preterm labor. 2. The duration of pregnancy is influenced by a positive culture result from genital tract swabs, regardless of the mechanism of preterm birth. 3. Further research should be conducted to effectively prevent preterm births.

**Keywords**: preterm birth; preterm premature rupture of membranes; spontaneous preterm labor; microorganisms in vaginal discharge; prematurity.

## INTRODUCTION

Preterm birth is a significant clinical issue in obstetrics. According to the World Health Organization, it is defined as the birth of a newborn between 22–37 weeks of gestation [1]. An estimated 13.4 million (95% credible interval ) newborn babies were born preterm (<37 weeks) in 2020 compared with 13.8 million in 2010 (9,8% of all births) worldwide. The global annual rate of reduction was estimated at –0.14% in 2010–2020 [2].

Preterm birth is associated with significant increases in neonatal and infant mortality and morbidity, as well as long-term adverse effects on physical and intellectual development. The most common complications of prematurity include respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, neonatal apnea, sepsis, and retinopathy of prematurity [1].

The immediate causes of preterm birth include spontaneous preterm labor (sPTL), preterm premature rupture of membranes (PPROM), and medically indicated preterm birth [3]. Inflammation within the reproductive organs is considered a major cause of preterm birth, accounting for 25–40% of preterm births. Inflammation caused by intrauterine infection triggers an inflammatory response in the body that leads to preterm labor and cervical dilation [4].

Pathogens identified in the reproductive tract of women experiencing preterm labor include: *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Fusobacterium*, *Gardnerella vaginalis*, *Peptostreptococcus*, and *Bacteroides* [5]. Pathogen entry into the uterine cavity activates the nonspecific immune system of the placenta and fetus. Microbial components, known as pathogen-associated molecular patterns (PAMPs), bind to various receptors, primarily Toll-like receptors (TLRs) found on monocytes, macrophages, neutrophils, dendritic cells, epithelial cells, and trophoblasts. Specific types of TLRs bind to corresponding PAMPs, initiating signal transduction that leads to the secretion of cytokines, chemokines, and interferons [6].

Major inflammatory mediators and risk factors for preterm birth include interleukins (IL): 1ß, IL-6, IL-8, and tumor necrosis factor-alpha, which stimulate C-reactive protein (CRP) production by hepatocytes. Interleukin 8 is also a potent chemokine that promotes inflammatory infiltration by mobilizing leukocytes [1].

The relationship between the etiological factor of infection and the degree of the induced inflammatory response is not fully understood. It is known that the immune response varies depending on whether the infection is caused by Gram+ bacteria, Gram– bacteria, atypical bacteria, fungi, or viruses. Early diagnosis, proper monitoring of the infectious process, and appropriate treatment of inflammation can significantly reduce the incidence of preterm birth [7, 8, 9].

The main aim of the study was to evaluate the impact of genital tract infections and the increase in CRP levels and leukocyte count in the blood of pregnant women on the occurrence of preterm labor and PPROM leading to preterm birth.

## MATERIALS AND METHODS

This retrospective study included 206 pregnant women, divided into 2 groups: the study group and the control group. The study group consisted of 133 women who delivered preterm, while the control group comprised 73 women who delivered at term. A thorough analysis of the medical records was conducted for the pregnant women in the study group who were hospitalized in the Clinical Obstetrics and Gynecology Department of Karol Marcinkowski University Hospital in Zielona Góra between 2016–2018. The patients were divided into 2 subgroups based on the predominant mechanism of preterm birth: the first subgroup included 52 women with preterm birth due to sPTL, and the second subgroup included 81 women with preterm birth due to PPROM. Vaginal and cervical swabs were analyzed, along with 2 primary inflammatory parameters: white blood cells (WBC) count and CRP levels.

To better establish the diagnostic value of WBC measurements in the subgroups, an analysis of the results from the control group patients hospitalized in 2019 was performed. These control group patients had no additional risk factors, delivered healthy newborns vaginally, and had uncomplicated pregnancies and deliveries.

The statistical evaluation results were reported for the entire study group and then divided into subgroups of patients with preterm labor and PPROM. Inclusion criteria for the study were the onset of preterm labor, characterized by the delivery of a newborn between 22–37 weeks of gestation, and PPROM, characterized by the premature rupture of membranes before 37 weeks of gestation.

The following factors were statistically analyzed for the study group: patient age, gestational age at hospital admission and on the day of delivery, obstetric history including preterm birth, PPROM, and miscarriage, comorbidities, smoking status, length of hospital stay, results of cervical swab for *U. urealyticum*, *M. hominis*, and *Chlamydia trachomatis*, vaginal swab for group B streptococcus (GBS) and other bacteria and fungi, 3 complete blood counts with automated differential performed sequentially on the day of hospital admission, on the day of swab collection, and on the first day postpartum, 3 CRP level tests taken in the same sequence, as well as pregnancy duration and newborn birth weight measured in grams immediately after birth.

In the control group, the analysis included 2 complete blood count tests with automated differential taken on the day of hospital admission and the first day postpartum, as well as the available CRP level measurement from the documentation.

Ethical approval for the study was obtained from the bioethics committee (KB-0012/07/02/2020/Z).

### Methodology for swab collection and culturing

In the study group, microbiological test results of swabs from the cervical canal and posterior vaginal fornix were evaluated. Negative results were defined as those with no growth of pathogenic bacteria or fungi, while positive results were classified as those with the presence of pathogenic microorganisms.

Swabs were collected during a gynecological examination by a specialist in gynecology and obstetrics, using sterile speculums and designated swab kits. Initial identification was conducted using Gram staining. For the detection of mycoplasmas and *C. trachomatis* antigens, samples were taken from the endocervical canal, and for the assessment of vaginal colonization, from the posterior vaginal fornix. Culturing was performed in the Microbiology Laboratory of the Karol Marcinkowski University Hospital in Zielona Góra.

To identify mycoplasmas, liquid broth medium IST2 was used. For detecting *C. trachomatis* antigens, the cassette-based quantitative test Chlamydia Antigen Test from Limarco was applied. Pathogen culturing from the posterior vaginal fornix was conducted using the following media from Biomerieux:

- Shaedler agar with vitamin K for anaerobic bacteria,
- MacConkey agar for Gram– bacteria,
- Sabouraud agar for fungi,
- chromogenic medium for *Candida* species,
- Columbia agar with 5% sheep blood for aerobic and facultative anaerobic hemolytic bacteria,
- VCA3 medium for *Neisseria gonorrhoeae*,
- agar medium for *G. vaginalis*,
- chromogenic medium for GBS.

### Automated differential blood count

Three consecutive results of blood morphology with an automated differential (from the day of hospital admission, the day of swab collection, and the first postpartum day) were analyzed using an Abbott analyzer. This allowed for the quantitative distribution of various leukocyte cell lines. Changes in the values of individual cell lines were analyzed. It should be noted that the reference values for WBC, used in the Diagnostic Laboratory at the Karol Marcinkowski University Hospital in Zielona Góra, refer to the European population and are as follows: leukocytes 4–10.2 thousand/μL, neutrophils 2–6.9 thousand/μL, lymphocytes 0.6–3.4 thousand/μL, monocytes 0.0–0.9 thousand/μL. Considering that there is no universally accepted upper limit for leukocyte values in pregnant women in the third trimester and immediately postpartum, absolute values of individual leukocyte lines were analyzed.

### Evaluation of C-reactive protein levels

The second inflammatory parameter assessed was CRP levels. Three CRP values were analyzed, obtained consecutively on the day of hospital admission, the day of swab collection, and the first postpartum day. The reference value for CRP is 0–5 mg/L. In this study, the cutoff value indicating infection was >5 mg/L [10, 11].

### Statistical analysis

Comparison of quantitative variables between 2 groups was performed using the Mann–Whitney test. Comparisons among 3 or more groups were performed using the Kruskal–Wallis test. When statistically significant differences were detected, *post-hoc* analysis was conducted using Dunn's test to identify significantly different groups.

The significance level was set at 0.05. Thus, all p-values <0.05 were interpreted as indicating significant relationships. A multivariate analysis of the independent influence of various variables on the quantitative variable was performed using linear regression. Results were presented as regression model parameter values with a 95% confidence interval. The analysis was conducted using R software, version 3.6.1: R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.

## RESULTS

The group of pregnant women with preterm birth due to spontaneous uterine contractions (sPTL) included 52 patients. The median age in this group was 30 years; the youngest patient was 21 years old, and the oldest was 37. The median gestational age at hospital admission was 32 weeks, with the shortest gestation being 20 weeks. The median gestational age at delivery was 33 weeks, with the shortest being 22 weeks. The patients in this group had an average of 2 pregnancies, with sporadic reports of previous preterm births and no reports of PPROM. The median length of hospitalization for this subgroup was 5 days, with the longest hospitalization lasting 97 days. Over 84% of patients reported no history of smoking (Tab. 1).

In contrast, the group of pregnant women with preterm birth due to PPROM included 81 patients. The median age in this subgroup was 30 years; the youngest patient was 19 years old, and the oldest was 44. The median gestational age at hospital admission was 32 weeks, with the shortest gestation being 19 weeks. The median gestational age at delivery was 33 weeks, with the shortest being 22 weeks. The patients in this subgroup had an average of 2 pregnancies, with sporadic reports of previous preterm births and no reports of PPROM. The median length of hospitalization for this subgroup was 5 days, with the longest hospitalization lasting 48 days. Over 88% of patients reported no history of smoking. Considering the parameters in Table 1, no statistically significant differences were noted between the 2 subgroups described ($p > 0.05$).

The control group consisted of 73 patients with no significant history of chronic diseases. No acute conditions were noted in these pregnant women during hospitalization. These women delivered naturally, at term, without complications. The median WBC value recorded at admission was 12,000/mL, and on the first postpartum day, it was 10,350/mL. The median CRP level was 3.4 mg/L (Tab. 2).

Based on the results of swabs from the cervical canal and posterior vaginal fornix of respondents with preterm birth, it was found that the most common pathogens in the reproductive tract of the study group were Gram+ bacteria, accounting for approx. 50.0% of infections. The second most frequently identified pathogens were mycoplasmas (22.56%), followed by Gram– bacteria (19.55%). Less frequently identified pathogens, in descending order of infection frequency, were *Candida* species and *Trichomonas vaginalis*. Group B streptococci, being part of the Gram+ bacteria group, were included in this group of microorganisms.

In the subgroup of patients with preterm birth due to sPTL, Gram+ bacteria were identified in 53.85% of cases. Mycoplasmas were the second most frequent pathogens (21.15%), followed by Gram– bacteria (17.31%). In the subgroup of pregnant women with preterm birth due to PPROM, Gram+ bacteria were found in 46.91% of swabs. Mycoplasmas were the second most frequent pathogens (23.46%), and Gram– bacteria were identified as the third most common pathogens in 20.99% of cases. No statistically significant differences were noted in the frequency of reproductive tract pathogens between the 2 subgroups ($p > 0.05$) – Table 3.

Based on the results of automated differential blood counts, the median WBC values for patients with preterm birth due to sPTL were as follows: at admission 12.85 thousand/μL, on the day of swab collection 12.9 thousand/μL, and on the first postpartum day 15.4 thousand/μL. From the perspective of infection, neutrophils – the most numerous immune cells responding to infection – had the following values: at admission 9.6 thousand/μL, on the day of swab collection 9.7 thousand/μL, and on the first postpartum day 12.6 thousand/μL. Similar results were obtained for patients with preterm birth due to PPROM, with WBC values as follows: at admission 12 thousand/μL, on the day of swab collection 12.9 thousand/μL, and on the

**TABLE 1. Study group characteristics**

| Parameters | | sPTL (n = 52) | PPROM (n = 81) | Total (n = 133) | p |
|---|---|---|---|---|---|
| Age (years) | mean ±SD | 30.13 ±4.72 | 30.25 ±5.23 | 30.20 ±5.02 | 0.882 |
| | median | 30.00 | 30.00 | 30.00 | |
| | quartiles | 27.00–34.00 | 27.00–34.00 | 27.00–34.00 | |
| Hbd at admission | mean ±SD | 30.94 ±4.07 | 30.65 ±4.60 | 30.77 ±4.38 | 0.911 |
| | median | 32.00 | 32.00 | 32.00 | |
| | quartiles | 28.75–34.00 | 28.00–34.00 | 28.00–34.00 | |
| Hbd at delivery | mean ±SD | 31.75 ±4.06 | 31.85 ±3.66 | 31.81 ±3.81 | 0.827 |
| | median | 33.00 | 33.00 | 33.00 | |
| | quartiles | 29.75–35.00 | 30.00–34.00 | 30.00–35.00 | |
| Number of pregnancies | mean ±SD | 2.15 ±1.35 | 2.20 ±1.45 | 2.18 ±1.41 | 0.872 |
| | median | 2.00 | 2.00 | 2.00 | |
| | quartiles | 1.00–3.00 | 1.00–3.00 | 1.00–3.00 | |
| Number of miscarriags | mean ±SD | 0.40 ±0.82 | 0.20 ±0.51 | 0.28 ±0.66 | 0.165 |
| | median | 0.00 | 0.00 | 0.00 | |
| | quartiles | 0.00–0.25 | 0.00 | 0.00–0.00 | |
| Number of preterm births | mean ±SD | 0.15 ±0.41 | 0.22 ±0.61 | 0.20 ±0.54 | 0.779 |
| | median | 0.00 | 0.00 | 0.00 | |
| | quartiles | 0.00–0.00 | 0.00–0.00 | 0.00–0.00 | |
| Days of hospitalization until delivery | mean ±SD | 8.67 ±13.89 | 9.43 ±11.60 | 9.14 ±12.50 | 0.84 |
| | median | 5.00 | 5.00 | 5.00 | |
| | quartiles | 2.00–10.25 | 2.00–12.00 | 2.00–11.00 | |
| Smoking status | no | 44.00 (84.62%) | 72.00 (88.89%) | 116.00 (87.22%) | 0.65 |
| | yes | 8.00 (15.38%) | 9.00 (11.11%) | 17.00 (12.78%) | |

sPTL – spontaneous preterm labor; PPROM – preterm premature rupture of membranes; p – for quantitative variables: Mann–Whitney U-test; for qualitative variables $\chi^2$ test or Fisher's exact test; Hbd – gestational age; SD – standard deviation

**TABLE 2. Control group characteristics**

| Parameters | n | No data | Mean | SD | Median | Min. | Max. | Q1 | Q3 |
|---|---|---|---|---|---|---|---|---|---|
| WBC at admisstion | 73 | 0 | 12.58 | 3.42 | 12.00 | 6.90 | 23.60 | 10.40 | 14.31 |
| NEU at admission | 73 | 0 | 9.66 | 3.31 | 8.90 | 4.50 | 19.00 | 7.50 | 11.51 |
| WBC 2 – 24 h after delivery | 73 | 0 | 15.00 | 3.69 | 13.85 | 8.60 | 25.20 | 12.80 | 16.70 |
| NEU 2 – 24 h after delivery | 73 | 0 | 11.55 | 3.39 | 10.35 | 6.00 | 20.70 | 9.50 | 13.00 |
| CRP | 69 | 4 | 4.89 | 4.75 | 3.40 | 0.40 | 26.00 | 2.10 | 5.20 |

WBC – leukocytes; NEU – neutrophils, CRP – C-reactive protein; SD – standard deviation

first postpartum day 15.55 thousand/μL. Neutrophil values were: at admission 9 thousand/μL, on the day of swab collection 10 thousand/μL, and on the first postpartum day 12.85 thousand/μL. Comparing the leukocyte and specific leukocyte line values between the 2 subgroups, no statistically significant differences were found ($p > 0.05$) – Table 4.

Table 5 compares the leukocyte counts of patients with preterm birth and those with full-term physiological birth. Analysis of WBC values at admission did not show significant differences between the preterm birth group and the full-term group (median 12.3 thousand/μL vs. 12.0 thousand/μL; $p > 0.05$). However, on the first day postpartum, patients with preterm birth had significantly higher WBC counts (median 15.4 thousand/μL vs. 13.85 thousand/μL; $p < 0.05$). Similar trends were observed for neutrophils: there were no statistical differences at admission, but on the first day postpartum, patients with preterm birth had significantly higher neutrophil counts compared to those with full-term births (12.7 thousand/μL vs. 10.35 thousand/μL; $p < 0.05$).

Analysis of CRP levels between the 2 subgroups within the study group revealed that CRP concentrations on the day of admission ($p = 0.004$) and on the day of swab collection

**TABLE 3. Microorganisms detected in the reproductive tract of patients with preterm birth**

| Microorganisms | Group | | | p |
|---|---|---|---|---|
| | sPTL (n = 52) | PPROM (n = 81) | total (n = 133) | |
| Gram+ | 28 (53.85%) | 38 (46.91%) | 66 (49.62%) | 0.547 |
| Gram– | 9 (17.31%) | 17 (20.99%) | 26 (19.55%) | 0.766 |
| Mycoplasmas (atypical bacteria) | 11 (21.15%) | 19 (23.46%) | 30 (22.56%) | 0.922 |
| *Escherichia coli* | 5 (9.62%) | 6 (7.41%) | 11 (8.27%) | 0.751 |
| *Klebsiella* | 1 (1.92%) | 3 (3.70%) | 4 (3.01%) | 1 |
| *Prevotella* | 4 (7.69%) | 7 (8.64%) | 11 (8.27%) | 1 |
| *Gardnerella* (bacterial vaginosis) | 1 (1.92%) | 1 (1.23%) | 2 (1.50%) | 1 |
| *Pseudomonas* | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 |
| Other Gram– | 0 (0.00%) | 3 (3.70%) | 3 (2.26%) | 0.28 |
| Other Gram+ | 21 (40.38%) | 31 (38.27%) | 52 (39.10%) | 0.951 |
| *Candida* | 6 (11.54%) | 9 (11.11%) | 15 (11.28%) | 1 |
| Other fungi | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 |
| *Chlamydia* | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 |
| *Trichomonas vaginalis* | 0 (0.00%) | 1 (1.23%) | 1 (0.75%) | 1 |

sPTL – spontaneous preterm labor; PPROM – preterm premature rupture of membranes; p – $\chi^2$ test or Fisher's exact test

**TABLE 4. Leukocyte counts in patients with preterm birth due to spontaneous labor and preterm premature rupture of membranes**

| Parameters | | Group | | p |
|---|---|---|---|---|
| | | sPTL (n = 52) | PPROM (n = 81) | |
| WBC at admission | mean ±SD | 13.36 ±3.79 | 12.90 ±3.32 | 0.493 |
| | median | 12.85 | 12.00 | |
| | quartiles | 11.07–14.80 | 10.80–15.20 | |
| WBC at the day of swab collection | mean ±SD | 13.60 ±4.23 | 13.92 ±5.23 | 0.986 |
| | median | 12.90 | 12.90 | |
| | quartiles | 11.05–14.80 | 10.90–15.40 | |
| WBC 24 h after delivery | mean ±SD | 16.29 ±5.65 | 17.29 ±7.06 | 0.645 |
| | median | 15.40 | 15.55 | |
| | quartiles | 12.80–19.05 | 12.88–20.00 | |
| NEU at admission | mean ±SD | 10.36 ±3.67 | 9.95 ±3.20 | 0.521 |
| | median | 9.60 | 9.00 | |
| | quartiles | 8.28–11.48 | 7.65–11.90 | |
| NEU at the day of swab collection | mean ±SD | 10.57 ±4.15 | 11.02 ±4.79 | 0.717 |
| | median | 9.70 | 10.00 | |
| | quartiles | 8.25–11.40 | 7.72–13.00 | |
| NEU 24 h after delivery | mean ±SD | 12.88 ±5.10 | 14.08 ±6.61 | 0.426 |
| | median | 12.60 | 12.85 | |
| | quartiles | 9.65–15.45 | 9.90–16.35 | |
| LIMF at admission | mean ±SD | 2.06 ±0.68 | 2.04 ±0.74 | 0.908 |
| | median | 2.00 | 2.00 | |
| | quartiles | 1.60–2.40 | 1.50–2.60 | |

**TABLE 4. Leukocyte counts in patients with preterm birth due to spontaneous labor and preterm premature rupture of membranes**

| Parameters | | Group | | p |
|---|---|---|---|---|
| | | sPTL (n = 52) | PPROM (n = 81) | |
| LIMF at the day of swab collection | mean ±SD | 2.07 ±0.69 | 1.98 ±0.78 | 0.419 |
| | median | 2.00 | 1.90 | |
| | quartiles | 1.60–2.45 | 1.40–2.45 | |
| LIMF 24 h after delivery | mean ±SD | 2.29 ±0.99 | 2.06 ±0.81 | 0.225 |
| | median | 2.10 | 2.00 | |
| | quartiles | 1.70–2.90 | 1.50–2.50 | |
| MONO at admission | mean ±SD | 0.78 ±0.27 | 0.73 ±0.30 | 0.252 |
| | median | 0.80 | 0.70 | |
| | quartiles | 0.60–0.92 | 0.60–0.90 | |
| MONO at the day of swab collection | mean ±SD | 0.79 ±0.28 | 0.77 ±0.40 | 0.305 |
| | median | 0.80 | 0.80 | |
| | quartiles | 0.60–0.95 | 0.50–0.90 | |
| MONO 24 h after delivery | mean ±SD | 1.10 ±0.75 | 1.01 ±0.42 | 0.63 |
| | median | 0.90 | 0.90 | |
| | quartiles | 0.80–1.25 | 0.79–1.20 | |

sPTL – spontaneous preterm labor; PPROM – preterm premature rupture of membranes; p – Mann–Whitney U-test; WBC – leukocytes; NEU – neutrophils; LIMF – lymphocytes; MONO – monocytes; SD – standard deviation

**TABLE 5. Comparison of leukocyte counts in patients with preterm birth and full-term physiological birth**

| Parameters | | Group | | p |
|---|---|---|---|---|
| | | preterm birth (n = 133) | full-term birth (n = 73) | |
| WBC at admission | mean ±SD | 13.08 ±3.51 | 12.58 ±3.42 | 0.312 |
| | median | 12.30 | 12.00 | |
| | quartiles | 10.80–14.90 | 10.40–14.31 | |
| WBC 24 h after delivery | mean ±SD | 16.90 ±6.54 | 15.00 ±3.69 | 0.042* |
| | median | 15.40 | 13.85 | |
| | quartiles | 12.85–19.75 | 12.80–16.70 | |
| NEU at admission | mean ±SD | 10.11 ±3.39 | 9.66 ±3.31 | 0.274 |
| | median | 9.50 | 8.90 | |
| | quartiles | 7.90–11.80 | 7.50–11.51 | |
| NEU 24 h after delivery | mean ±SD | 13.61 ±6.07 | 11.55 ±3.39 | 0.011* |
| | median | 12.70 | 10.35 | |
| | quartiles | 9.75–16.15 | 9.50–13.00 | |

p – Mann–Whitney U-test; WBC – leukocytes; NEU – neutrophils; SD – stamdard deviation
* statistically significant relationship ($p < 0.05$)

($p = 0.042$) were significantly higher in the subgroup with preterm birth due to sPTL. The CRP levels in the sPTL group were 6.15 mg/L and 6.3 mg/L respectively, compared to 3.9 mg/L and 4 mg/L in the PPROM group – Table 6.

C-reactive protein levels on the day of hospital admission ($p = 0.03$) and on the day of swab collection ($p = 0.003$) were also significantly higher in the group of patients with preterm birth who had positive genital tract swab cultures, with values of 4.7 mg/L and 5.7 mg/L respectively, compared to CRP levels in patients with negative swab cultures, which were 3.1 mg/L and 3 mg/L, respectively (Tab. 7).

In the subgroup of respondents with preterm birth due to sPTL who had positive genital tract swab cultures, significantly higher CRP levels were observed in all 3 measurements ($p < 0.05$) compared to patients with negative swab cultures. However, no statistically significant differences in CRP levels were found between the 2 groups of patients with preterm birth due to PPROM ($p > 0.05$) – Table 8.

**TABLE 6. C-reactive protein levels in patients with preterm birth due to spontaneous uterine contractions and preterm premature rupture of membranes**

| Parameters | | Group | | p |
|---|---|---|---|---|
| | | sPTL (n = 52) | PPROM (n = 81) | |
| CRP at admission | mean ±SD | 10.69 ±13.36 | 6.63 ±10.93 | 0.004* |
| | median | 6.15 | 3.90 | |
| | quartiles | 3.20–10.20 | 1.90–6.50 | |
| CRP at the day of sway collection | mean ±SD | 12.91 ±18.73 | 11.46 ±29.9 | 0.042* |
| | median | 6.30 | 4.00 | |
| | quartiles | 3.20–10.60 | 2.10–7.60 | |
| CRP – 24 h after delivery | mean ±SD | 25.82 ±37.52 | 38.28 ±55.36 | 0.781 |
| | median | 8.00 | 14.30 | |
| | quartiles | 4.60–23.85 | 2.42–50.25 | |

sPTL – spontaneous uterine contractions; PPROM – preterm premature rupture of membranes; p – Mann–Whitney U-test; SD – standard deviation
* statistically significant relationship (p < 0.05)

**TABLE 7. Comparison of C-reactive protein levels in patients with preterm birth, considering genital tract swab culture results**

| Parameters | | Total swab | | p |
|---|---|---|---|---|
| | | negative | positive | |
| CRP at admission | mean ±SD | 4.19 ±3.16 | 9.59 ±13.59 | 0.03* |
| | median | 3.10 | 4.70 | |
| | quartiles | 1.88–6.25 | 2.40–9.55 | |
| CRP at the day of swab collection | mean ±SD | 4.17 ±3.25 | 14.77 ±29.61 | 0.003* |
| | median | 3.00 | 5.70 | |
| | quartiles | 1.80–5.50 | 2.70–14.30 | |
| CRP at delivery | mean ±SD | 18.24 ±31.51 | 38.21 ±53.50 | 0.067 |
| | median | 5.40 | 13.00 | |
| | quartiles | 2.70–17.9 | 3.82–51.08 | |

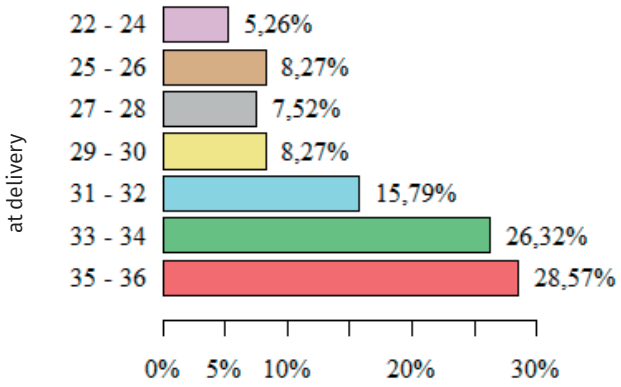
p – Mann–Whitney U-test; SD – standard deviation
* statistically significant relationship (p < 0.05)

**TABLE 8. Comparison of C-reactive protein levels in patients with preterm birth due to spontaneous uterine contractions and preterm premature rupture of membranes, considering genital tract swab culture results**

| Parametrs | | sPTL | | PPROM | |
|---|---|---|---|---|---|
| | | negative (n = 12) | positive (n = 40) | negative (n = 22) | positive (n = 59) |
| CRP at admission | mean ±SD | 4.24 ±3.19 | 12.62 ±14.62 | 4.17 ±3.22 | 7.54 ±12.56 |
| | median | 3.40 | 7.65 | 2.75 | 4.00 |
| | quartiles | 1.45–6.12 | 3.77–12.82 | 2.10–6.22 | 1.90–6.40 |
| p | | 0.014* | | 0.584 | |
| CRP at the day of swab collection | mean ±SD | 4.24 ±3.19 | 15.57 ±20.68 | 4.12 ±3.37 | 14.21 ±34.68 |
| | median | 3.40 | 7.10 | 2.70 | 4.55 |
| | quartiles | 1.45–6.12 | 4.10–20.00 | 2.10–5.40 | 2.10–11.10 |
| p | | 0.012* | | 0.114 | |
| CPR at delivery | mean ±SD | 3.83 ±4.54 | 29.08±39.20 | 22.08 ±34.60 | 43.23 ±59.72 |
| | median | 2.50 | 8.60 | 6.00 | 17.90 |
| | quartiles | 0.65–5.68 | 4.85–28.65 | 3.30–22.00 | 1.90–61.70 |
| p | | 0.036* | | 0.371 | |

p – Mann–Whitney U-test; SD – standard deviation; sPTL – spontaneous uterine contractions; PPROM – preterm premature rupture of membranes
* statistically significant relationship (p < 0.05)

A very important parameter assessed in the study was the duration of pregnancy in patients with preterm birth. It was found that the minimum duration of pregnancy was 22 weeks and the maximum was 36 weeks, with an average duration of 31.81 weeks (SD = 3.81). The majority of patients gave birth at 35–36 weeks of gestation, while the fewest gave birth at 22–24 weeks (Fig. 1).




Hbd – gestational age

**FIGURE 1.** Duration of pregnancy in patients with preterm birth

Analyzing the results of women with preterm birth in terms of the impact of genital tract infections on the duration of pregnancy showed that both women in the Scs group (p = 0.044) and the PPROM group (p = 0.009) with negative genital tract swab cultures gave birth significantly later, with a median gestational age at delivery of 34 weeks, compared to women in the same subgroups with positive swab cultures, who had a median gestational age at delivery of 32 weeks (Tab. 9).

An attempt was also made to analyze the impact of genital tract infections on the birth weight of newborns. In the subgroup of women with preterm birth due to sPTL, no statistically significant differences were found in the birth weight of preterm infants between mothers with negative and positive genital tract swab cultures (p = 0.123). However, statistically significant differences (p = 0.023) were observed in the subgroup of women with preterm birth due to PPROM, both with negative and positive genital tract swab cultures. The median birth weight of newborns of mothers with negative swab cultures was 2247.5 g, whereas for mothers with positive swab cultures, it was 1940 g (Tab. 10).

## DISCUSSION

In the 21st century, one might assume that fundamental medical issues, such as diagnosing and treating infections caused by well-known pathogens, should no longer pose challenges in clinical practice. However, the reality is different, with estimates suggesting that 25–40% of preterm births are caused by intrauterine infection [1, 5]. According to data from the United States, presented by Kalinka and Bitner [5], approx. 7% of preterm infants are born before 28 weeks of gestation, about 18% between 29–32 weeks, and 75% between 33–36 weeks. In our study, 21% of preterm infants were born before 28 weeks, 24% between 29–32 weeks, and 55% between 33–36 weeks. This discrepancy may be explained by the fact that the study group consisted of selected patients with numerous exclusion criteria.

The first issue that arises is the diagnosis of genital tract infections in pregnant women. Literature indicates that the most commonly identified pathogens in the amniotic fluid of patients with intrauterine infections are genital mycoplasmas and *Fusobacterium*. Additionally, GBS, *Escherichia coli*, and *G. vaginalis* are frequently identified [1]. Vaginal swabs also commonly detect *Prevotella* and *Bacteroides* species. In our study, the most frequently identified pathogens were Gram+ bacteria (including GBS and other streptococci) and mycoplasmas, followed by Gram– bacteria (including *Fusobacterium*, *E. coli*, *Bacteroides*, and *Prevotella*). It should be noted that identification was only based on cervical and vaginal swab cultures, as molecular methods could not be applied.

In the study group, intrauterine infection was not diagnosed even once. The available data did not include amniotic fluid culture results because the patients did not meet the criteria for Triple I Suspected [8]. Although leukocytosis was present, the pregnant women were afebrile, no purulent discharge from the cervical canal was observed during gynecological examination, and imaging studies did not provide grounds for diagnosing fetal tachycardia.

In the subgroups of patients categorized based on the mechanism of preterm birth, there were no statistically significant differences in the frequency of pathogen identification. It is worth noting that pathogens typically associated with PPROM, including *C. trachomatis*, *T. vaginalis*, and *N. gonorrhoeae*, were identified in only 1 patient in the study group.

**TABLE 9. Duration of pregnancy in patients with preterm birth due to spontaneous uterine contractions and preterm premature rupture of membranes considering the results of bacteriological tests**

| Parametr | | sPTL | | PPROM | |
|---|---|---|---|---|---|
| | | negative (n = 12) | positive (n = 40) | negative (n = 22) | positive (n = 59) |
| Duration of pregnancy | mean ±SD | 33.92 ±1.98 | 31.10 ±4.31 | 33.27 ±3.37 | 31.32 ±3.65 |
| | median | 34.00 | 32.00 | 34.00 | 32.00 |
| | quartiles | 32.75–36.00 | 27.75–35.00 | 33.00–35.75 | 29.00–34.00 |
| p | | 0.044* | | 0.009* | |

p – Mann–Whitney U-test; SD – standard deviation; sPTL – spontaneous uterine contractions; PPROM – preterm premature rupture of membranes
* statistically significant relationship (p < 0.05)

**TABLE 10. Birth weight of newborns from mothers with preterm birth due to spontaneous uterine contractions and preterm premature rupture of membranes considering the results of bacteriological tests**

| Parametr | | sPTL | | PPROM | |
|---|---|---|---|---|---|
| | | negative (n = 12) | positive (n = 40) | negative (n = 22) | positive (n = 59) |
| Birth weight of the fetus at delivery (g) | mean ±SD | 2301.67 ±504.41 | 1839.75 ±784.35 | 2182.73 ±715.45 | 1806.19 ±742.47 |
| | median | 2215.00 | 1965.00 | 2247.50 | 1940.00 |
| | quartiles | 2086.25–2508.75 | 1162.5–2583.75 | 2077.50–2635.00 | 1215.00–2315.00 |
| p | | 0.123 | | 0.023* | |

p – Mann–Whitney U-test; SD – standard deviation; sPTL – spontaneous uterine contractions; PPROM – preterm premature rupture of membranes
* statistically significant relationship (p < 0.05)

Among the Gram+ bacteria identified, GBS was included. Their classification as commensal or colonizing pathogens can evoke differing opinions. In the mid-1990s, they were considered human commensals [9]. However, in the 1970s, studies clearly linked neonatal sepsis incidence with vaginal colonization by GBS [10]. Additionally, data linking vaginal or cervical colonization with preterm birth are now clear, as demonstrated by an extensive meta-analysis conducted by Bianchi-Jassir et al. [11]. Assessing the impact of GBS on CRP levels and WBC counts (assuming they are colonizing bacteria, not pathogenic) compared to other Gram+ bacteria is beyond the scope of this work. It would be interesting to consider how the immune system, which does not recognize colonizing organisms as pathogens, changes its response pattern and begins to eliminate them once it considers them pathogenic; however, this question remains unanswered.

Among the pathogenic microorganisms identified in the study group was *G. vaginalis*, a Gram-variable bacterium. Its cell wall contains a peptidoglycan layer similar to Gram+ bacteria but is thin and stains variably with Gram's method, sometimes appearing as Gram+ and other times as Gram– [12]. Its identification did not influence the analysis results for the respective pathogen groups, as it was only cultured twice from mixed etiology swabs.

A significant aspect of studies on microorganisms causing preterm birth is the limitations of classical culture on media. As many pathogens do not grow outside the host organism or die quickly, it is uncertain whether patients in the study group with negative swab cultures and CRP >5 mg/L were not actually infected. Similarly, it is unclear whether patients with negative swab cultures and insignificant CRP levels were truly uninfected. Identification using molecular methods helps minimize this problem, although it only recognizes microorganism species whose genomes are at least partially known.

Our study showed that both subgroups of patients, those with sPTL and those with PPROM, were relatively homogeneous. The women had similar obstetric histories, were of similar age, began hospitalization at a similar stage of pregnancy, and delivered at a similar gestational age. White blood cells values in both subgroups did not show statistically significant differences. Conversely, CRP levels were significantly higher in the sPTL subgroup than in the PPROM subgroup, both on the day of hospital admission and the day of swab collection.

Further analysis showed that in the sPTL subgroup with positive swab results, CRP levels were significantly higher in all 3 measurements compared to pregnant women with negative swab results. This correlation was not found in the PPROM subgroup, where positive swab results did not cause a significant increase in CRP levels in any of the 3 measurements compared to the PPROM subgroup with negative swab results. It is worth noting that many studies have highlighted the relationship between high CRP levels, preterm uterine contractions, and the effectiveness of tocolytic treatment [13, 14]. This relationship is logically related to increased production of prostaglandins and IL-1β and decreased tissue progesterone activity, occurring at the cellular level before CRP production by hepatocytes [1, 15, 16].

Interestingly, patients with PPROM initiated labor without showing preterm uterine contractions, and their CRP levels were significantly lower regardless of whether the swab was positive. This may suggest a cause-and-effect relationship: an increase in CRP levels causes increased uterine activity, and the conditions for its occurrence were not met in patients with PPROM. Literature data provide numerous insights into the relationship between PPROM and infection and CRP levels. Some studies describe CRP as a weak predictor of intrauterine infection [17, 18], while others show a strong correlation [19, 20]. It is difficult to find studies attempting to determine a direct correlation between CRP levels and PPROM, regardless of suspected infection.

The control group included patients without any additional medical history that could affect WBC and CRP levels. These women delivered healthy newborns naturally, without complications. The WBC values on the day of admission in the control group did not differ significantly from those recorded in the study group. However, the WBC values obtained day after delivery were significantly higher in the study group. Additionally, the median CRP levels in the control group were 3.4 mg/L, with an average value of 4.89 mg/L, which does not exceed the level considered indicative of infection. This supports the hypothesis that WBC is of limited utility in predicting preterm birth and genital tract infections based on positive swab results in preterm birth patients.

The use of CRP as an inflammatory marker in patients with preterm birth requires further discussion. C-reactive protein levels increase in response to injury, infection, or

inflammation [21]. It is a sensitive but nonspecific marker. This is why pregnant women with autoimmune disease, active cancer, and suspected or confirmed infections other than genital tract infections were excluded from the study. Patients with liver diseases and kidney failure were also excluded. In the first case, CRP synthesis may be impaired, and in the second, its metabolism and excretion may be abnormal [1]. A limitation of the study is the lack of data on incidental CRP levels in the study group patients before pregnancy and during pregnancy before the onset of preterm labor.

Next, the impact of positive bacteriological test results on pregnancy duration was analyzed in the sPTL and PPROM subgroups. In both cases, pregnancies lasted significantly longer in patients with negative genital tract swab cultures. These results are not surprising, as many studies have already found a connection between abnormal vaginal and cervical flora and preterm birth [22]. In the presented study, we compared 2 groups of preterm birth patients, which supports the statement that a positive genital tract swab result further shortens the duration of pregnancy in preterm birth patients.

Given this context, a natural question arises: does a genital tract infection, identified by a positive bacteriological test result, also affect the birth weight of preterm infants? The data here were inconclusive. In the sPTL subgroup, preterm infants of mothers with negative swab results weighed an average of 2301.67 g, while those of pregnant women with positive swab results weighed 1839.75 g, yielding a statistically insignificant result with a test probability of 0.123. Conversely, in the PPROM subgroup, a positive genital tract swab result caused a statistically significant decrease in the birth weight of newborns, with a p-value of 0.023 (average weights of 1806.19 g and 2182.73 g). It is clear that intrauterine infection affects birth weight as it is closely associated with the diagnosis of preterm birth [1, 18]. In the presented study, only preterm newborns were compared, and the obtained results do not allow for definitive conclusions.

Additional commentary is warranted for CRP levels in the entire study group with negative bacteriological test results, as well as in the subgroups of sPTL and PPROM patients without infection. C-reactive protein levels in these groups had medians below 5 mg/L for measurements taken on the day of hospital admission and the day of swab collection. This is an important observation, indicating the usefulness of serial CRP measurements in excluding infection in women with preterm birth.

As can be seen, single measurements of the nonspecific parameter CRP appear to be of little significance. The study also showed that this acute-phase protein is not useful in diagnosing infections in pregnant women with PPROM.

## CONCLUSIONS

1. Serial measurements of acute-phase protein levels can be a very useful parameter for assessing inflammation and excluding infection within the genital tract in pregnant women. Additionally, fluctuating CRP levels are associated with preterm uterine contractions.
2. The duration of pregnancy is influenced by positive genital tract swab culture results, regardless of the mechanism of preterm birth.
3. Further research is needed to effectively prevent preterm births.

## STUDY LIMITATIONS

One limitation of the study was the inability to use molecular methods for pathogen identification, which may have led to an underestimation of the number of patients with genital tract infections. Additionally, the timing of sample collection for laboratory tests varied (different times of day and night), as many patients were admitted on an emergency basis, which could have influenced the results obtained.

Another limitation was the challenge in precisely determining the onset of the factors causing sPTL or PPROM and the time elapsed from their occurrence to the patient's hospital admission, despite meticulous medical histories. Consequently, the duration of the infection processes in the women remains unclear. This uncertainty impacts the laboratory results obtained and may affect the genital tract swab culture outcomes, not just the specific infectious factor.

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