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COTELEA Veronica

THE ROLE OF POLYFUNCTIONAL IMMUNOMODULATORY PROTEINS IN PREMATURE BIRTH

321.15 – OBSTETRICS AND GYNECOLOGY

Summary of the Doctor of Medical Sciences Thesis

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Conducător

Dondiuc Iurie, dr. hab. șt. med., conf. univ.

Membrii comisiei de îndrumare

Gudumac Valentin, dr. hab. șt. med., prof. univ.

Corolcova Natalia, dr. șt. med., conf. univ.

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Membrii comisiei de doctorat:

Moșin Veaceslav, dr. hab. șt. med., prof. univ.,
USMF „Nicolae Testemițanu", Disciplina de obstetrică și ginecologie,
Departamentul Obstetrică și Ginecologie - președinte;

Dondiuc Iurie, dr. hab. șt. med., conf. univ.,
USMF „Nicolae Testemițanu",
Disciplina de obstetrică și ginecologie,
Departamentul Obstetrică și Ginecologie - conducător științific;

Gudumac Valentin, dr. hab. șt. med., prof. univ.,
USMF „Nicolae Testemițanu",
Catedra de medicină de laborator - referent oficial, membru al comisiei de îndrumare;

Cernețchi Olga, dr. hab. șt. med., prof. univ.,
USMF „Nicolae Testemițanu",
Disciplina de obstetrică și ginecologie,
Departamentul Obstetrică și Ginecologie - referent oficial;

Rotaru Marin, dr. hab. șt. med., prof. univ.,
IMSP Institutul Mamei și copilului - referent oficial;

Mișina Ana, dr. hab. șt. med., conf. univ.,
IMSP Institutul Mamei și copilului - referent oficial.

Președinte Comisiei de doctorat,
Moșin Veaceslav
dr. hab. șt. med., prof. univ.

Conducător științific,
Dondiuc Iurie
dr. hab. șt. med., conf. univ.

Autor,
Cotelea Veronica

CONTENT

INTRODUCTION

Current situation and importance of the problem

Premature birth (PN) is one of the greatest challenges of contemporary obstetrics, a global perinatal health problem, representing the main cause of morbidity, neonatal and infant mortality worldwide. According to statistical data, in the last decade the frequency of prematurity has maintained a stable trend at the global level, moreover, in some highly developed countries, the rate of this obstetric pathology has increased [19, 22, 25].

Currently, contemporary methods of prognosis and prevention of prematurity are widely used in obstetric practice. However, despite this fact, approximately 1 million newborns die annually due to complications associated with prematurity, and millions of surviving premature babies remain disabled throughout their lives [21, 24]. Thus, the World Health Organization (2023) established new strategies for the prevention of preterm birth by deepening research in the field of identifying the mechanisms underlying preterm labor, as well as detecting effective predictors of this obstetric pathology.

The literature data report that in the structure of premature birth 2/3 represent spontaneous premature birth [14, 15, 16], and scientific research in the field of contemporary obstetrics states that premature birth represents a syndrome that includes multiple causes and associated etiologies [1, 2, 8, 13]. Thus, among the certain causes of spontaneous premature birth, inflammatory ones have been demonstrated, especially intraamniotic inflammation [17, 18]. Intraamniotic inflammation can occur in two different contexts: through intraamniotic microbial invasion, while the second occurs in the absence of microbial substrate and is associated with a local increase in endogenous danger signals, thus called sterile inflammation [5, 9, 10].

It is important to note that a growing number of scientific publications emphasize that these two inflammatory conditions have similar clinical outcomes, and the correlation between the innate immune system and the evolution of sterile or nonsterile intraamniotic infection is crucial [3, 17, 18].

Recent studies have found a link between the immune system and the development of sterile or nonsterile inflammation (intraamniotic infection). Therefore, knowledge of the changes in the innate immune system that occur in the case of intraamniotic infection and sterile intraamniotic inflammation is essential for understanding the mechanisms of development of preterm birth and determining the correct management of patients at risk of prematurity [4, 6, 7, 11, 12]. And early identification of changes in the innate immune system would provide the possibility of a prognosis of the development of sterile or infectious (nonsterile) inflammation associated with the risk of preterm birth, would provide the possibility of developing

an appropriate obstetrical conduct, which may contribute to improving perinatal outcomes [20, 23, 25].

Summarizing the above, we conclude that preterm birth represents an important perinatal problem due to the complexity and subtlety of the polyetiological mechanisms underlying it. And a more detailed understanding of the changes in the maternal immune system offers the possibility of developing new prognostic methods, which will facilitate the timely prevention of preterm birth and the development of therapeutic strategies that will improve the expected perinatal outcomes [20, 23, 25].

Therefore, the polyetiological and complex features underlying preterm birth have generated the development of the present study, defining the purpose and objectives of the research.

Purpose of the study. The study was conducted to assess the role of polyfunctional immunomodulatory proteins in premature birth triggered to optimize obstetric management and improve perinatal outcomes.

Objectives of the study:

1. Study the evolution of pregnancy, birth and perinatal outcomes in women with spontaneous premature birth.
2. Assessment of serum values of polyfunctional immunomodulatory proteins (LF and α2 – MG) in spontaneous premature birth.
3. Assessment of serum values of proinflammatory cytokines (Il-1β, Il-6 and TNF-α) in spontaneous premature birth.
4. Evaluation of the correlation between serum values of polyfunctional immunomodulatory proteins and proinflammatory cytokines in spontaneous premature birth.
5. Determining potential predictors for preterm birth with the development of an algorithm to optimize obstetric management and improve perinatal outcomes of pregnant women at risk of preterm birth.

General research methodology. The research was organized and conducted based on the Department of Obstetrics and Gynecology within the Nicolae Testemițanu State University of Medicine and Pharmacy, in obstetric wards 1, 2, 3 of the Perinatology Center within the Gheorghe Paladi Municipal Clinical Hospital IMSP and the Biochemistry Laboratory of the Nicolae Testemițanu State University of Medicine and Pharmacy, with permission from the administration of the respective institutions for the collection and processing of primary data during the years 2018-2022. The research project and the study protocol were approved by the Research Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy (minutes no. 16 of November 21, 2017) and by the Bioethics Committee of the Gheorghe Paladi Municipal Clinical Hospital IMSP (minutes no. 1-A of February 2, 2018).

Scientific novelty and originality: The study elucidated the peculiarities of the evolution of pregnancy, childbirth and perinatal outcomes in pregnant women with spontaneous preterm birth. In the study, the serum values of LF and α2 – MG as well as proinflammatory cytokines (Il-1β, Il-6 and TNF-α) were assessed as a whole, as well as the correlation of these inflammatory markers in women with spontaneous preterm birth. A predictive model of preterm birth was developed, based on the anamnesis, comorbidities of women whose pregnancy was complicated by preterm birth. Based on the results obtained, a diagnostic and management algorithm for pregnant women at risk of spontaneous preterm birth was proposed to optimize clinical management and improve perinatal outcomes.

The theoretical significance: The results of this study make important contributions to the understanding of the pathogenetic mechanisms of preterm birth, confirming the determining role of intrauterine inflammation and immunological imbalance in the initiation of preterm labor. The analysis of serum biomarkers, especially Lactoferrin (LF), α2-Macroglobulin (α2-MG) and proinflammatory cytokines (IL-1β, IL-6, TNF-α), provided new insights into the screening and prevention of prematurity, paving the way for the implementation of more efficient methods for the identification and management of patients at high risk of preterm birth.

The applicative value of the study: Integrating biomarker testing into prenatal screening allows the identification of high-risk pregnant women before clinical signs of preterm labor become evident.

Monitoring serum levels of LF and α2-MG could help obstetricians to establish the prognosis of pregnancy progression and adjust the individualized care plan.

The predictive models developed in the current research can be used to guide clinical interventions, ensuring a better allocation of medical resources and avoiding excessive treatment of low-risk patients.

The personalized therapeutic protocol proposed based on this study could lead to more effective prevention strategies, through the administration of antenatal corticosteroids to correctly selected patients, the use of anti-inflammatory therapies and preventive antibiotic therapy.

Identification of serum biomarkers of prematurity can optimize the monitoring of high-risk pregnancies, allowing for early diagnosis, better targeted treatments and the reduction of unnecessary medical interventions.

The implementation of an obstetric management algorithm, based on biomarkers of polyfunctional immunomodulatory proteins, proposed following the study, could improve diagnostic accuracy, guide treatment and reduce neonatal complications associated with prematurity.

Implementation of scientific results: Based on the study, a predictive model of preterm birth was proposed, which was implemented in the Perinatological Center of

the PMI *Gheorghe Paladi* Municipal Clinical Hospital. Based on the study, a Methodological Recommendation was developed and implemented in the teaching process of the Departament of Obstetrics and Gynecology of *Nicolae Testemițanu* PI SUMPh, as well as in the curent activites of PMI *Gheorghe Paladi* Municipal Clinical Hospital.

Approval of scientific results. The basic principles of the work were reported and discussed in various national and international scientific forums:

• Conference Days of the State University of Medicine and Pharmacy "Nicolae Testemițanu". Chișinău, October 15-19, 2018.

• The 7th International Medical Congress for Students and Young Doctors MedEspera. Chișinău, May 3-5, 2018.

• The 15th International Congress for Medical Students and Young Doctors. Romania, Iasi, May 3-6, 2018.

• The 8th International Medical Congress for Students and Young Doctors MedEspera. Chișinău, September 24-26, 2020.

• National Congress of Fetal and Neonatal Medicine with international participation. Romania, Bucharest, May 11-13, 2023.

• The 28th EBCOG CONGRESS. Poland, Krakow, 18-20 May, 2023.

• European Exhibition of Creativity and Innovation EUROINVENT l5th edition, 26-28 May 2023.

• The 37th Balkan Medical Week ”PERSPECTIVES OF BALKAN MEDICINE IN THE POST COVID-19 ERA”. Chisinau, 7-9 June 2023.

• National scientific and practical conference “DAYS OF ACADEMICIAN GHEORGHE PALADI ON HIS 95TH ANNIVERSARY”. Chisinau, 17 May 2024.

• 13th National Congress of the Romanian Society of Obstetrics and Gynecology. Romania, Bucharest, 21-23 November 2024.

Publications on the topic of the thesis. Based on the study materials, 25 works were published, of which 1 article in national journals, 4 articles in international peer-reviewed journals, 2 articles without co-authorship, 7 abstracts in the proceedings of national and international scientific conferences, 1 innovator's certificate, 1 certificate of registration of objects of copyright and related rights, 4 communications at international and 2 national scientific forums, 5 international posters, 1 methodological recommendation.

Thesis volume and structure. The thesis is presented on 162 typewritten pages and consists of: introduction, literature review (chapter 1), research material and methods (chapter 2), three chapters of own results (chapters 3, 4, 5), synthesis of the obtained results, general conclusions, practical recommendations, bibliography with 203 sources, 8 annexes, information on the use of research results. The work contains 20 tables, 22 figures.

Keywords: premature birth, innate immunity, inflammation, sterile inflammation, polyfunctional immunomodulatory proteins, lactoferrin, α2 – macroglobulin, morbidity, mortality.

1. PREMATURE BIRTH, A CURRENT PROBLEM IN CONTEMPORARY OBSTETRICS. THE ROLE OF THE INNABITANT IMMUNE SYSTEM IN THE TRIGGERING OF PREMATURE BIRTH

The chapter is a synthesis of bibliographic data that covers: the current state of the problem of premature birth, configurations related to etiopathogenesis and risk factors, classification criteria, the modern concept of predicting premature birth, the impact of given pathology on perinatal outcomes.

It is well known that the evolution of a pregnancy is directly dependent on the maternal immunological status, thus at the moment of premature birth triggering against the background of an inflammatory process, the immune system is activated with the catalysis of the immune response and as a result the change in the ratio of pro- and anti-inflammatory elements that lead to compromising the evolution of the pregnancy.

Unfortunately, despite the fact that the risk factors of premature labor are well known, at present, there are no effective methods of prediction, prevention or treatment of spontaneous premature births, and the efforts of developed countries by applying technologies that increase the survival rate of premature children do not improve the impact of the disease worldwide, thus increasing the morbidity of these children at a distance.

Thus, a better understanding of the mechanisms of the immune system will allow to clarify the pathogenesis of premature birth. Certainly, new prognostic methods can be developed, which will facilitate the timely prevention of premature birth with the development of therapeutic strategies that will improve perinatal outcomes.

Premature birth is a current problem of contemporary obstetrics, therefore conditioning the sequence of research, in order to decrease the rate of perinatal morbidity and mortality.

2. RESEARCH MATERIALS AND METHODS

The research was organized and carried out based on the Department of Obstetrics and Gynecology within the IP USMF Nicolae Testemițanu, in obstetric wards 1, 2, 3 of the Perinatology Center within the IMSP Gheorghe Paladi Municipal Clinical Hospital and the Biochemistry Laboratory of the IP USMF Nicolae Testemițanu, with permission from the administration of the respective institutions for the collection and processing of primary data during the years 2018-2022.

A prospective cohort study was planned and carried out, in which cases with spontaneous premature birth were examined.

The required number of research units was estimated based on the formula (1):

$$n = \frac{1}{(1-f)} \times \frac{2(Z_\alpha + Z_\beta)^2 xP(1-P)}{(P_o - P_1)^2}$$

(1)

Therefore, the optimal number of respondents of a research group, with a representative value, is no less than 65 patients. A total of 150 women were selected in the research and after selection, according to the inclusion and exclusion criteria as well as the refusal to participate, we reached the representative figure of 130 patients, who were distributed into two groups with a 1:1 ratio, as follows: the research group (L1) included 65 respondents who gave birth prematurely; the control group (L0) included 65 respondents who gave birth at term. Inclusion and exclusion criteria were applied to select the patients from the research.

Inclusion criteria in the study:

1. Gestational age between 22+0 and 36+6 weeks admitted to obstetric wards with spontaneous premature birth;
2. Spontaneous pregnancy;
3. Monofetal pregnancy;
4. Spontaneous premature birth;
5. Patient age ≥ 18 years;
6. Informed consent, in written form, for participation in the study.

Exclusion criteria from the study:

1. Gestational age between 22+0 and 36+6 weeks admitted to obstetric wards with induced premature birth;
2. Pregnancy resulting from the application of assisted reproductive technologies;
3. Multiple pregnancy;
4. Presence of congenital malformations of the fetus;
5. Serious extragenital pathology (decompensated) of the patient;
6. Acute infectious pathology at the time of birth;
7. Iatrogenic premature birth;
8. Prolonged aliquid period ≥ 18 hours;
9. Patient age ≤ 18 years;
10. Lack of informed consent to participate in the study.

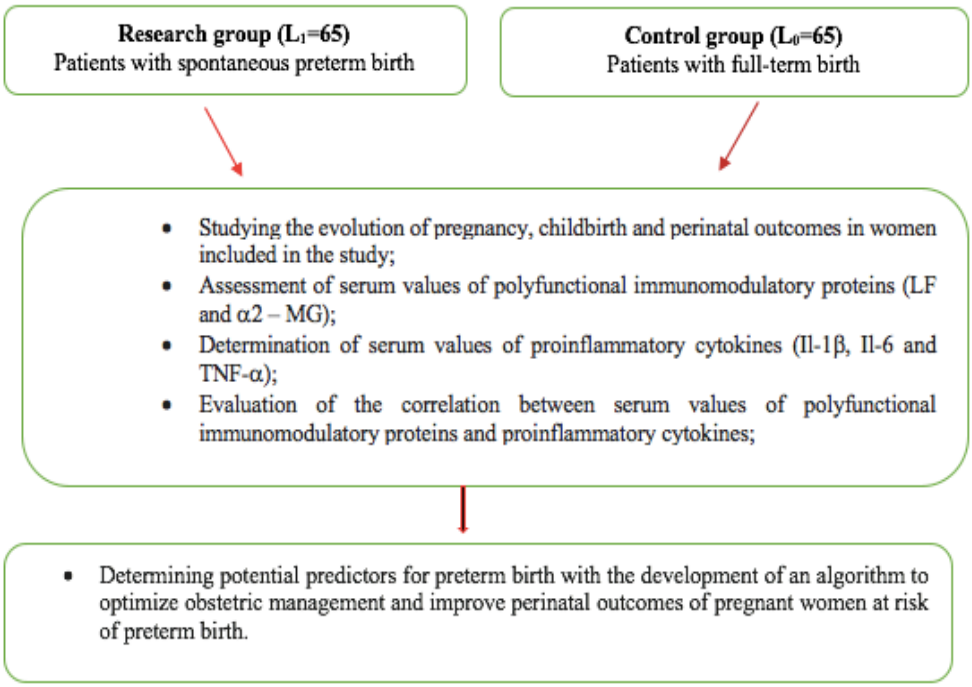


Figure 1. **Study design**

Following the study and extraction of data from the medical documentation (perinatal record, patient observation sheet, newborn sheet), a complex examination of the patient and the newborn was performed, which included the clinical and paraclinical aspects.

Clinical examination (collection of anamnestic and clinical data through standardized interviewing, determination of the patient's general objective and obstetric-gynecological status, assessment of anthropometric data, gestational age and newborn's condition at birth (Apgar score). Paraclinical and laboratory examination were performed in the Biochemical Laboratory of the IP USMF "Nicolae Testemițanu" by detecting maternal and, respectively, fetal serum values of polyfunctional immunomodulatory proteins such as LF and α2 – MG, as well as assessing the serum level of proinflammatory cytokines (Il-1β, Il-6 and TNF-α).

Thus, for the assessment of the proposed biochemical markers, 10 ml of peripheral venous blood was taken from the respondents from the cubital vein in the first period of birth. Subsequently, the obtained blood was centrifuged, and the obtained serum served as research material for determining the parameters targeted in the research. The determination of polyfunctional immunomodulatory proteins was performed using ELISA-sandwich enzyme-linked immunosorbent assay kits from AESKU.DIAGNOSTICS GmbH & Co.KG (Germany) for LF and CLOUD-CLONE Corp. (USA) for α2 – MG according to the instructions attached to the reagent set. The assessment of proinflammatory cytokines was performed using sandwich

immunosorbent assay kits using mono- and polyclonal antibodies from VECTOR-BEST (Russia) according to the instructions attached to the reagent set.

The results obtained were included in the specially developed and applicable questionnaire for both groups, which included eleven compartments and 139 questions (Annex 1). The agreement to participate in the research was obtained directly from the participants (information and acceptance forms).

The collected data were analyzed using the RStudio version 4.1.3 (rstudio-com.netlify.app) and IBM SPSS Statistics version 26.0 (https://www.ibm.com/support/pages/ibm-spss-statistics-26-documentation) programs, which ensured the validity and reproducibility of the procedures performed. Statistical processing of the data obtained by applying specific statistical operations.

3. CLINICAL AND HISTORICAL FEATURES, THE EVOLUTION OF PREGNANCY, BIRTH AND ESTABLISHMENT OF RISK FACTORS FOR PREMATURE BIRTH

3.1. Anamnestic and clinical-evolutionary particularities of pregnant women with premature birth

In the context of the established objectives, the anamnestic and clinical-evolutionary peculiarities of the study participants were evaluated. Following the analysis of the data obtained regarding the age of the pregnant women included in the study, we found that PB developed more frequently in the age range over 30 years (49.2%; 95% CI: 37.9-61.2%), and in the control group, birth occurred more frequently in the age range 21-30 years (55.4%; 95% CI: 43.3-67.0%). However, analyzing the coefficient of variation of the age of the study participants from both groups, no statistical difference was detected regarding this indicator, with $\chi^2$2df = 3.465, p = 0.177, which indicates a homogeneity of the groups according to this criterion. In the study group, respondents predominantly came from urban areas 92.3% (95% CI: 84.0-97.0%), $\chi^2$1df =4.127, p=0.042. Examination of the socioeconomic status (marital status, educational level, workplace) of the research participants did not establish statistically significant differences between the groups (p>0.05). Evaluation of the frequency of harmful factors among pregnant women who had premature birth compared to pregnant women who gave birth at term found that, of all the factors studied, only psychoemotional overload at work had a statistically significant incidence among women who gave birth prematurely with $\chi^2$1df =4.795, p=0.029. Studying behavioral risk factors noted a high incidence of harmful habits in women who gave birth prematurely, thus 10.8% (95% CI: 4.9-20.0%) were active smokers and mentioned that they use from 4 to 22 cigarettes per day. The analysis of the distribution of pregnant women according to parity criteria determined that the majority of women who gave birth prematurely are secundiparous 43.1% (95% CI: 31.6-55.2%), $\chi^2$2df =3.143, p=0.208. It is noteworthy that in the research group there was a high frequency

of imminent premature birth in the history of previous pregnancies, with a rate of 16 (24.6%) cases, the differences being statistically significant ($\chi^2$1df = 18.246, p=0.0001; 95% CI: 15.4-36.0%). An important aspect of the obstetric history presented the recurrence rate of premature birth for future pregnancies. As a result, the research results demonstrated that 7 women or 10.8% (95% CI: 4.9-20.0%) of the research group were diagnosed with premature birth in previous pregnancies. In the control group, no pregnant woman had a history of premature birth, the differences being statistically significant ($\chi^2$1df 7.398, p=0.007; 95% CI: 4.9-2.0%). In the structure of extragenital pathology, we found that, in the majority of cases, the evolution of pregnancy in a pregnant woman in the study group occurred against the background of a chronic pathology preexisting pregnancy, especially of inflammatory-infectious origin. In particular, in the structure of extragenital pathology diagnosed in patients in the research group, nephrourinary tract diseases (chronic pyelonephritis, bacteriuria, chronic cystitis, renal colic, nephrolithiasis) were recorded more often, with a rate of 21 or 32.3% (95% CI: 21.9-44.3%) cases in L1, compared to 9 or 13.8% (95% CI: 7.1-23.7%) cases in L0, with $\chi^2$1df 6.240, p=0.012.

The research examined the evolution, clinical conduct and complications that occurred during the current pregnancy, finding that every 2nd woman in the study group had low serum hemoglobin values, with $\chi^2$2df 7.488, p=0.024. Likewise, an increased frequency of hyperemesis gravidarum (p=0.001), imminent miscarriage that affected every 3rd pregnant woman in the study group (p=0.0001) and imminent premature birth (p=0.0001) was detected.

Therefore, every 2nd–3rd woman in the study group had at least one episode of imminent premature birth. According to the data of the current study, we note that no statistically significant differences were found between the number of medical abortions (p=0.199), spontaneous abortions (p=0.300) and stagnant pregnancies (p=0.518) (table 1).

Evaluating the peculiarities of the extragenital anamnesis in the women included in the study, we determined that in the majority of cases, the evolution of pregnancy in a pregnant woman in the study group occurred against the background of a chronic pathology preexisting pregnancy, especially of inflammatory-infectious origin.

Thus, in the structure of extragenital pathology, that of the urinary tract (chronic pyelonephritis, bacteriuria, chronic cystitis, renal colic, nephrolithiasis) was recorded more often, with a statistically significant incidence among women who gave birth prematurely (p=0.026).

Table 1. **Obstetric history of patients in the research groups**

Criteria	Nr.	Loturile de studiu: The research group, L_1 n_1=65 abs.	The research group, L_1 n_1=65 % (95% IÎ)	Control group, L_0 n_2=65 abs.	Control group, L_0 n_2=65 % (95% IÎ)	χ^2	p
Medical abortion	1	7	10,8% (4,9-20,0%)	5	7,7% (3,0-16,0%)	4,649	0,199
	2	2	3,1%(0,6-9,5%)	0	0,0%	4,649	0,199
	3	2	3,1% (0,6-9,5%)	0	0,0%	4,649	0,199
Miscarriage	1	8	12,3% (6,0-21,9%)	4	6,2% (2,1-14,0%)	2,410	0,300
	2	0	0,0%	1	1,5% (0,2-7,0%)	2,410	0,300
Stagnant pregnancy	1	3	4,6% (1,3-11,8%)	2	3,1% (0,6-9,5%)	2,273	0,518
	2	1	1,5 (0,2-7,0%)	0	0,0%	2,273	0,518
	3	1	1,5% (0,2-7,0%)	0	0,0%	2,273	0,518
Ectopic pregnancy		1	1,5% (0,2-7,0%)	2	3,1% (0,6-9,5%)	0,341	0,559
History of imminence preterm birth		16	24,6% (15,4-36,0%)	0	0,0%	18,246	0,0001
Historu of preterm birth		7	10,8% (4,9-20,0%)	0	0,0%	7,398	0,007
Cesarean section		3	4,6% (1,3-11,8%)	1	1,5% (0,2-7,0%)	1,032	0,310

At the same time, the study data reveal a statistically significant difference (p=0.003) between the groups in terms of exacerbation of inflammatory pathology preexisting pregnancy. Similarly, there was an increased incidence in patients with premature birth, compared to women who gave birth at term, of infectious-inflammatory pathology of the respiratory system (p=0.001), nephrourinary (0.026) and genital organs (p=0.001) (table 2).

Table 2. **Distribution of cases according to infectious-inflammatory pathology of pregnant women**

Infectios-inflammatory pathology		*Lots*				χ^2	p
		$Lotul_1$, n=65		$Lotul_0$, n=65			
		abs.	%	abs.	%		
Respiratory diseases	Trimester I	2	3,1	1	1,5	18,667	0,0001
	Trimester II	7	10,8	0	0		
	Trimester III	11	16,9	1	1,5		
Nephrourinary diseases	Trimester I	1	1,5	3	4,6	9,290	0,026
	Trimester II	7	10,8	4	6,2		
	Trimester III	13	20,0	3	4,6		
Genital tract disorders	Trimester I	0	0	1	1,5	16,321	0,001
	Trimester II	6	9,2	1	1,5		
	Trimester III	10	15,4	0	0		

Therefore, according to the data presented, each of the infectious-inflammatory pathologies associated with pregnancy was identified as a determining factor for premature birth, the data being statistically significant, and the highest rate of exacerbation of pre-existing inflammatory pathology in the research group was recorded in the second and third trimesters of pregnancy, a fact that can certainly be correlated with the mechanism of inducing NP.

3.2. Particularities of childbirth and the postnatal period in pregnant women included in the study

Analysis of the peculiarities of the course of childbirth in women from the study groups, the method of pregnancy termination, the incidence and structure of cesarean section, complications that occurred during labor, the characteristics of newborns, as well as the structure of perinatal morbidity and mortality. In the base group, the rate of cesarean section birth was significantly higher compared to women who gave birth at term with $\chi^2 1df = 5.190$, $p = 0.004$, it is necessary to mention that the most frequent indication for cesarean section was abnormal fetal presentations. The conduct of childbirth in respondents with premature birth included labor analgesia more frequently, compared to the control group – 17 (26.2%) vs 5 (7.7%) cases, with $\chi^2 2df = 10.317$, $p = 0.006$. Thus, we can conclude that the need for more frequent application of labor analgesia was associated in the vast majority of cases with cesarean section, which had a higher incidence in the study group. No statistically significant differences were found between the groups regarding the duration of the alichidian period, which was: up to 12 hours - 61 (93.8%) cases in the research group vs 60 (92.3%) cases in the control group and 12 – 18 hours - 4 (6.2%) cases in the study group vs 5 (7.7%)

cases in the control group, with $\chi^2$1df = 0.119 p = 0.730. The impact of the studied pathology on perinatal outcomes remains colossal.

Thus, it was of interest to evaluate the characteristics of children born to mothers included in the research. To assess the condition of newborns at birth, the Apgar score was used at the first and fifth minute of life (figure 2).

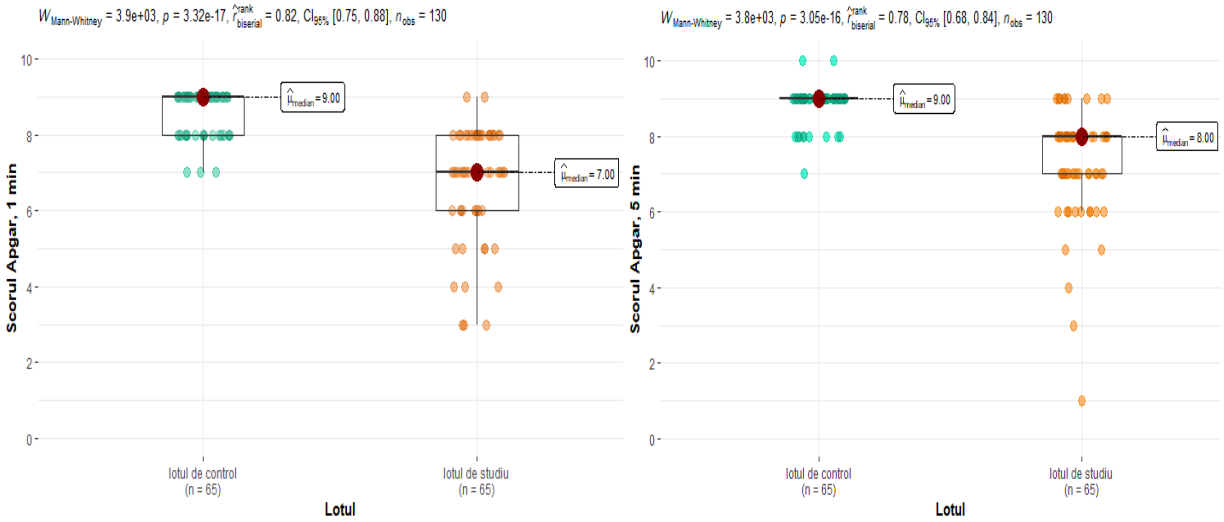


Figure 2. **Distribution of groups according to Apgar score at minute 1 and minute 5 of life of newborns (points)**

Based on the data obtained, the frequency of newborn asphyxia was evaluated, which found that, in the first minute of life, the Apgar score was 3-9 points, μ median=7 in the research group vs 7-9 points, μ_{median}=9 in the control group (rrank biserial=0.82, 95% CI: 75.0-88.0%), and at the 5th minute the Apgar score was 1-9 points, μ_{median}=8 in the research group vs 7-10 points with μ_{median}=9 in the control group (rrank biserial=0.78, 95% CI: 68.0-84.0%).

A factor with a direct influence on perinatal indices is the body weight of newborns at birth. As a result of the study, we found that most children born in the study group had a body weight of 700–3330 g; μmedian=2440 g vs 2100–4491 g; μmedian=3440 g in the control group (p=0.0001). It was interesting to study the number of children by sex, so the distribution in both groups studied was homogeneous: female newborns – 37 or 56.9% (95% CI: 44.8-68.4%) in the base group vs 39 or 60.0% (95% CI: 47.9-71.3%) in the control group; male newborns – 28 or 43.1% (95% CI: 31.6-55.2%) in the baseline group vs 26 or 40.0% (95% CI: 28.7-52.1%), with $\chi^2$1df = 0.127, p=0.859.

In the process of evaluating newborns, it is necessary to mention that, in the study group, a high incidence of various pathological conditions was attested (table 3).

Among the pathologies diagnosed in newborns from mothers with NP, neonatal respiratory distress syndrome was frequently attested - 21 or 32.3% (95% CI: 21.9-44.3%) with $\chi^2$1df = 25.045, p=0.0001 in the study group vs. no cases in the control group. At the same time, an increased incidence of intrauterine infection was

determined in the group of children born to mothers who gave birth prematurely - 17 or 26.2% (95% CI: 16.7-37.7%) with $\chi^2$1df = 19.558, p=0.0001 in the study group vs. no cases in the control group. Similarly, a high incidence of congenital pneumonia was observed - 14 or 21.5% (95% CI: 12.9-32.6%) with $\chi^2$1df = 15.690, p=0.0001 in the study group vs no cases in the control group.

Table 3. **Frequency of neonatal pathology in newborns from the studied groups**

Variabile	**Lot_1, n=65 (abs., %)**	**Lot_0, n=65 (abs., %)**	**χ^2**	**p**
Neonatal respiratory distress syndrom	21 (32,3%)	0 (0%)	25,045	0,0001
Congenital pneumonia	14 (21,5)	0 (0%)	15,690	0,0001
Intrauterine infection	17 (26,2)	0 (0%)	19,558	0,0001
Neonatal sepsis	6 (9,2%)	0 (0%)	6,290	0,037
Septicemia	2 (3,1%)	0 (0%)	2,031	0,476
Mortality (late)	2 (3,1%)	0 (0%)	2,031	0,476

Another important aspect related to the complications of preterm birth is the presence of signs of prematurity in newborns, which can directly affect their morbidity. Thus, we found that children in the research group have the following signs of prematurity: lanugo – 51 children or 78.5% (95% CI: 67.4-87.1%) with $\chi^2$1df = 83.924, p=0.0001 in the study group vs. no cases in the control group; underdeveloped adipose tissue - 43 children or 66.2% (95% CI: 54.1-76.8%) with $\chi^2$1df = 64.253, p=0.0001 in the study group vs. no cases in the control group; soft and deformed earlobes - 39 children or 60.9% (95% CI: 47.9-71.3%) with $\chi^2$1df = 55.714, p=0.0001 in the study group vs no case in the control group; nails not covering the nail bed - 46 children or 70.8% (95% CI: 59.0-80.7%) with $\chi^2$1df = 71.190, p=0.0001 in the study group vs no case in the control group; decreased skin turgor - 38 children or 58.5% (95% CI: 46.3-69.9%) with $\chi^2$1df = 53.696, p=0.0001 in the study group vs no case in the control group. Therefore, children born prematurely in most cases, regardless of the degree of prematurity, have specific signs of underdevelopment and, therefore, maladaptation that have induced the need for additional postpartum care over a longer period of time.

The results regarding the duration of hospitalization of patients highlighted a series of deviations: in the study group it varied between 3 and 294 days/bed, 46 (70.8%) cases vs 1 and 3 days/bed, 65 (100%), with $\chi^2$1df=71.190, (95% CI: 59.0-80.7%), p=0.0001. Therefore, patients with premature birth spent a longer period of time in the hospital, the cause being neonatal morbidity in premature newborns, who required additional, long and expensive postpartum care.

4. DYNAMICS OF VALUES OF POLYFUNCTIONAL IMMUNOMODULATORY PROTEINS AND PROINFLAMMATORY CYTOKINES IN PREMATURE BIRTH

4.1. Particularities of serum values of polyfunctional immunomodulatory proteins in women included in the study

In the research conducted, with the aim of evaluating the role of polyfunctional immunomodulatory proteins as a pathogenetic link in the development of premature birth, the serum level of Lactoferrin (LF) and α2 – Macroglobulin (α2 – MG) in maternal blood was assessed. Following the analysis performed, we determined that the maternal serum values of LF in the research group varied within the limits of 0.02 – 10.90 U/ml, the average value being – μmedian= 0.99 U/ml. In the control group, the average value of LF in maternal serum was – μmedian= 40.68 U/ml, varying between 0.78 – 62.73 U/ml, the effect size being large, (biserial rrank =0.98, 95%CI 0.97, 0.99; p<0.001) (figure 3).

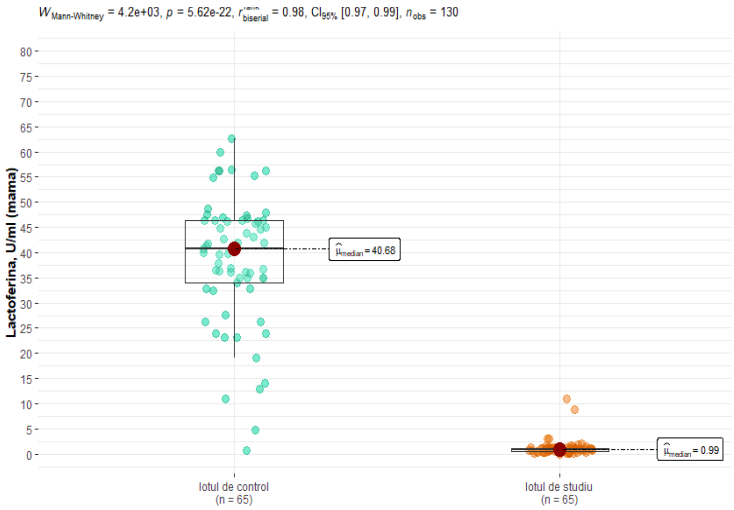


Figure 3. **Serum levels of LF in women included in the study**

The results of the study show that the mean serum value of maternal LF fluctuates considerably depending on the gestational age at which PB occurred. Thus, the mean serum value of LF was significantly lower in women with extremely premature births (< 28 weeks of amenorrhea) with μ_{median}= 0.29 U/ml, being 2 times lower than in the group of very premature births (28-31+6 weeks of amenorrhea) with μ_{median}= 0.67 U/ml and almost 5 times lower than in the case of moderately premature births - μ_{median}= 1.41 U/ml.

Another important biochemical indicator of the current study was α2–MG. Thus, the mean level of α2–MG in maternal serum was μ_{median}= 41.91 pg/ml in the research group, compared to μ_{median}= 1.10 pg/ml in the control group, and the effect sizes were large ($r_{rank\ biserial}$=0.97, 95%CI -0.98, -0.96 p<0.001), varying in both study groups (L1 – 5.06-99.88 pg/ml vs L0 – 0.76-80.84 U/ml) (figure 4).

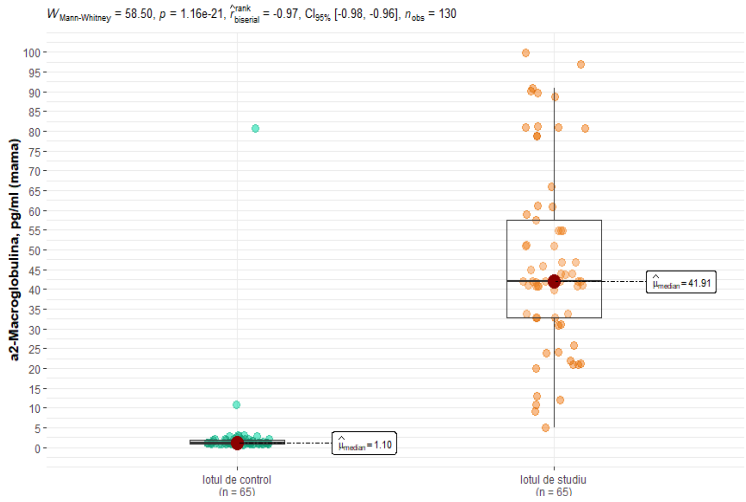


Figure 4. **Serum levels of α2–MG in women included in the study**

It is important to mention that the research identified significantly higher mean serum α2–MG values in women with extremely premature births (< 28 weeks of amenorrhea) - μ_{median}= 85.89 pg/ml, being over 2 times higher than in moderately premature births - μ_{median}= 39.13 pg/ml, which signifies an activation of the innate immune response by modulating inflammation.

4.2. Assessment of serum levels of proinflammatory cytokines in study participants

In the study conducted, we analyzed the serum level of proinflammatory cytokines (IL-1β, Il-6 and TNF-α) to assess the severity of the inflammatory syndrome in women with premature birth. Therefore, the respondents included in the research, in accordance with the proposed purpose, were determined the serum value of IL-1β, which determined a mean value of μ_{median}=3.99 pg/ml in the research group, compared to μ_{median}= 1.08 pg/ml in the control group, the effect sizes ($r_{rank\ biserial}$=0.84, 95%CI -0.89, -0.77 p<0.001), varying significantly in both study groups (L1 – 0.99-10.60 pg/ml vs L0 – 0.05-3.16 pg/ml). At the same time, the research results reveal that the mean serum value of IL-1β was significantly higher in women with extremely premature births (< 28 weeks of amenorrhea) - μ_{median}=8.39 pg/ml, being over 2 times higher than in the case of moderately premature births (32-37 weeks of amenorrhea) - μ_{median}=3.68 pg/ml and almost double compared to the group of very premature births (28-31+6 weeks of amenorrhea) - μ_{median}=4.81 pg/ml, which characterizes the severity of the inflammatory process which is more noticeable in the subgroup of extremely premature births, p<0.001.

The mean maternal serum IL-6 value was: μ_{median}=51.90 pg/ml in the research group, compared to μmedian=21.51 pg/ml in the control group, the effect sizes ($r_{rank\ biserial}$=0.85, 95%CI -0.89, -0.78 p<0.001), varying significantly in both study groups (L1 – 0.99-192.93 pg/ml vs L0 – 9.65-137.97 pg/ml). Likewise, the research results reveal that the mean maternal serum value of IL-6 was significantly higher in women

with extremely premature births (< 28 weeks of amenorrhea) - μ_{median}=144.06 pg/ml, being almost 3 times higher than in the case of moderately premature births (32-37 weeks of amenorrhea) - μ_{median}=52.11 pg/ml and higher than in the group of very premature births (28-31+6 weeks of amenorrhea) - μ_{median}=124.73 pg/ml, which characterizes the severity of the inflammatory process, especially in the case of the subgroup of extremely premature births, p<0.001.

The mean value of TNF-α in maternal blood was: μ_{median}=26.54 pg/ml in the research group, compared to μ_{median}=12.40 pg/ml in the control group, the difference being large (biserial rrank =-0.78, 95%CI -0.85, -0.69 p<0.001), varying significantly in both study groups (L1 – 12.51-121.72 pg/ml vs L0 – 9.23-45.42 pg/ml). The research results reveal that the mean serum value of TNF-α was significantly higher in women with extremely premature births (< 28 weeks of amenorrhea) - μ_{median}=71.55 pg/ml, being almost 3 times higher than in the case of moderately premature births (32-37 weeks of amenorrhea) - μ_{median}=25.77 pg/ml and higher than in the group of very premature births (28-31+6 weeks of amenorrhea) - μ_{median}=60.28 pg/ml, which characterizes the severity of the inflammatory process, especially in the case of the subgroup of extremely premature births.

4.3. Correlational analysis of polyfunctional immunomodulatory proteins and proinflammatory cytokines

The correlation analysis, performed to determine a link between maternal serum levels of LF and IL-1β in the study group, established a negative correlation coefficient (rs=-0.396 95%CI -0.608, -0.133; p=0.001), the Pearson correlation being inversely proportional, which demonstrates that these criteria correlate in the opposite direction: the lower the serum level of LF, the higher the serum level of IL-1β. The correlation analysis performed to determine the relationship between maternal serum levels of LF and IL-6 in the study group established a negative correlation coefficient (rs=-0.377 95%CI -0.580, -0.148; p=0.002), the Pearson correlation being inversely proportional, which demonstrates that these criteria correlate in the opposite direction: the lower the serum level of LF, the higher the serum level of IL-6. The correlation analysis, performed with the aim of determining the link between maternal serum levels of LF and TNF-α in the study group, also established a negative correlation coefficient (rs=-0.450 95%CI -0.654, -0.212; p<0.002), the Pearson correlation being inversely proportional, which demonstrates that these criteria correlate in the opposite direction: the lower the serum level of LF, the higher the serum level of TNF-α (table 4).

Table 4. **Correlation analysis (ρ Spearman) for polyfunctional immunomodulatory proteins and pro-inflammatory cytokines in maternal serum in the study group**

	IL-1β, pg/ml	IL-6, pg/ml	TNF-α, pg/ml
LF, U/ml	-0,396**	-0,377**	-0,450**
Sig. (2-tailed)	0,001	0,002	<0,001
95% CI	-0,608	-0,580	-0,654
	-0,133	-0,149	-0,212
α2-MG, pg/ml	0,289*	0,609**	0,522**
Sig. (2-tailed)	0,019	<0,001	<0,001
95% CI	0,028	0,406	0,291
	0,525	0,757	0,693

Following the correlation analysis performed to determine a link between maternal serum levels of α2-MG and IL-1β in the study group, a positive correlation coefficient was established (rs=0.289 95%CI 0.028, 0.525; p=0.019), the Pearson correlation being direct, which demonstrates that these criteria correlate directly proportionally: the higher the serum level of α2-MG, the higher the serum level of IL-1β (table 4).

The data reflecting the correlation analysis to determine a link between maternal serum levels of α2-MG and IL-6 in the study group established a positive correlation coefficient (rs=0.609 95%CI 0.406, 0.757; p<0.001), the Pearson correlation being direct, which demonstrates that these criteria correlate in a directly proportional sense: the higher the serum level of α2-MG, the higher the serum level of IL-6. Likewise, the data reflecting the analysis for determining a link between maternal serum levels of α2-MG and TNF-α in the study group established a positive correlation coefficient (rs=0.522 95%CI 0.291, 0.693; p<0.001), the Pearson correlation being direct, which demonstrates that these criteria correlate directly proportionally: the higher the serum level of α2-MG, the higher the serum level of TNF-α.

5. DETERMINING POTENTIAL PREDICTORS FOR PREMATURE BIRTH WITH THE DEVELOPMENT OF THE ALGORITHM FOR OPTIMIZING OBSTETRICAL MANAGEMENT AND IMPROVING PERINATAL OUTCOMES

5.1. Development of clinical predictive models for preterm birth

One of the objectives of the research was to develop predictive models for the development of preterm birth based on anamnestic data, pregnancy progression and associated pathology. Thus, to answer the basic research question, the following predictive models were developed: The proposed clinical predictive model 1 is a model developed based on anamnestic data and pregnancy progression that included the covariates: iron deficiency anemia in pregnancy, imminent miscarriage, the presence of vulvovaginitis and exacerbation of preexisting pathology during pregnancy. To validate this predictive model, the following hypotheses were formulated: Null hypothesis – information about the progression of pregnancy, the presence of pregnancy-associated pathology and/or exacerbation of preexisting chronic pathology cannot predict the probability of preterm birth better than a model that is based only on a constant (a single pathology); and Alternative hypothesis – information about the course of pregnancy, the presence of pregnancy-related pathology and/or exacerbation of pre-existing chronic pathology may predict the probability of preterm birth better than a model that is based only on a constant.

For the "Clinical Predictive Model 1", confirmatory data were obtained that demonstrated its ability to predict the probability of premature birth, the null hypothesis was rejected (Omnibus Test of Model Coefficients (χ2df4 = 63.311, $p<0.001$), and further analysis revealed the following characteristics of the validated model. The determination indicator, Nagelkerke R Square, showed the value 0.533 (53.3%), which means that the predictors (covariates in this model) explained more than half (53.3%) of the dependent dispersive variables. And the calibration indicator (Hosmer–Lemeshow test) showed a non-significant value, χ2df4 = 0.864, $p = 0.930$ – an indicator of sufficient calibration, that is, the score has a good ability to determine whether the pregnant woman will give birth at term or prematurely with the ability to stratify risks. The discrimination indicators in the table classification, namely specificity and sensitivity, were equal to 69.2% and 90.8%, respectively, the summary percentage (global) being appreciated at 80.0%. The results were obtained at the critical point value of 0.5 (figure 5).

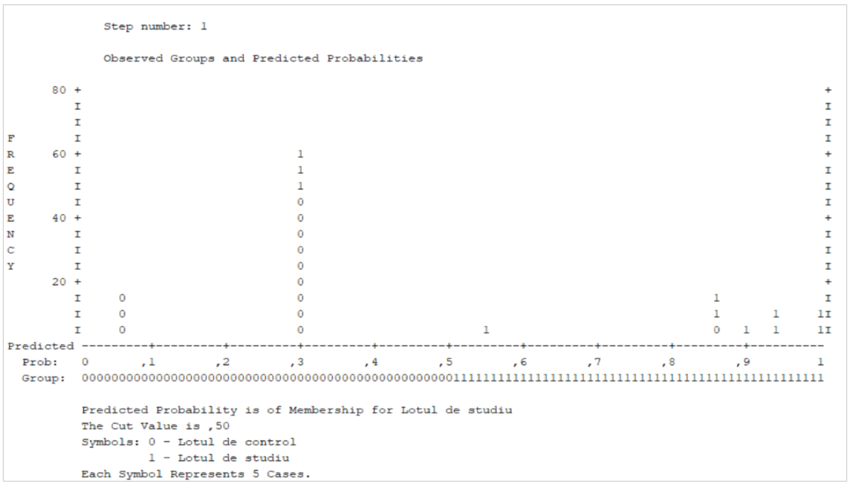


Figure 5. **Preterm birth probability classification chart for Clinical Predictive Model 1**

The model included the constant (B = 1.114), of which: low serum hemoglobin value (B = -1.977) with (χ^2_{df1} = 7.576, p<0.001) (95% CI: 0.034-0.566%), imminent miscarriage (B = 2.671) with (χ^2_{df1} = 14.599, p<0.001) (95% CI: 3.673-56.914%), vulvovaginitis during pregnancy (B = 3.553) with (χ^2_{df1} = 9.908, p<0.002) (95% CI: 3.822-319.159%) as well as exacerbation of chronic pathology pre-existing pregnancy (B = 3.040) with (χ^2_{df1} = 9.379, p<0.002) (95% CI: 2.987-146.195%). Stability analysis by resampling the proposed model for determining the probability of premature birth using the bootstrapping method (1000 samples) showed that the coefficient is stable, significant and the sign remains unchanged.

The area under the ROC curve, for Clinical Predictive Model 1, was 0.852 (95% CI 0.786, 0.918) and significantly different from the value of 0.5 ($p < 0.001$) (Figure 6).

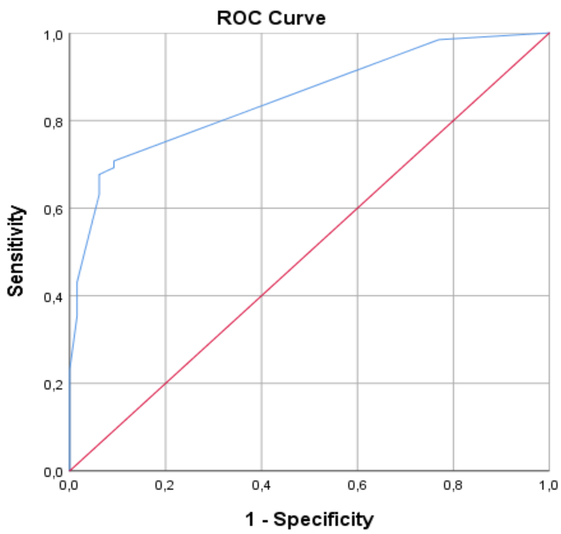


Figure 6. **ROC curve for estimating the probability of premature birth of the Clinical Predictive Model 1**

Therefore, the developed model has the predictive capacity for preterm birth having 4 predictors as follows. Iron deficiency anemia in pregnancy is a predictor that

increases the probability of preterm birth with OR=0.139 (95%CI 0.34, 0.566). The imminence of spontaneous abortion increases the probability of preterm birth with OR=14.458 (95%CI 3.673, 56.914). Another predictor – the presence of vulvovaginitis during pregnancy increases the probability of preterm birth with OR=34.927 times (95%CI 3.822, 319.159), the last predictor being the exacerbation of chronic pathology preexisting pregnancy with OR=20.897 (95%CI 2.987, 146.195).

The developed clinical predictive model 2 was supplemented in comparison with the clinical predictive model 1 with several covariates, including: the woman's age over 30 years and the existence of inflammatory-infectious pathology of the respiratory system. Thus, the development of the clinical predictive model 2 allowed to supplement information about the pregnant woman and the evolution of the current pregnancy, with the detailing of the relationships within the eventual equation and, as a result, improved the developed model. The clinical predictive model 2 demonstrated the ability to predict premature birth, the null hypothesis being rejected (Omnibus Test of Model Coefficients (χ2df6 = 90.309, p<0.001), and the subsequent analysis revealed the following characteristics of the validated model. The determination indicator, Nagelkerke R Square, showed the value of 0.668 (66.8%), which indicates that the predictors explained/covered 2/3 of the dispersion of the dependent variable of interest. It is important to note that the value of this model is higher than in the previous model. The calibration indicator (Hosmer–Lemeshow test) showed a non-significant value, χ2df6 = 2.102, p = 0.910, which means a sufficient calibration indicator, that is, the score has a good ability to determine whether the pregnant woman will give birth at term or prematurely with the ability to stratify risks. The discrimination indicators in the classification table, namely specificity and sensitivity, were equal to 81.5% and 92.3%, respectively, the summary (global) percentage was estimated at 86.9%. The results were obtained at the critical point value of 0.5 (figure 7).

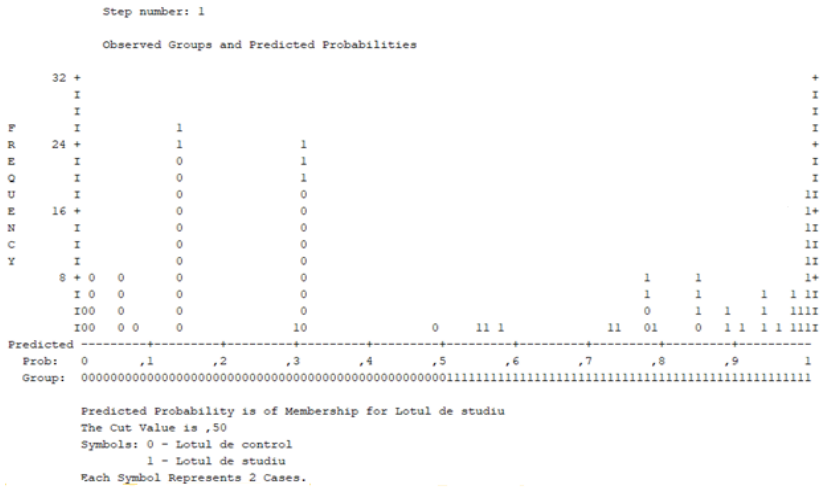


Figure 7. **Preterm birth probability classification chart for Clinical Predictive Model 2**

The model included the constant (B = -1.758) with the following variables: iron deficiency anemia in pregnancy (B = -2.124) with (χ2df1 = 6.494, p<0.011) (95% CI: 0.023-0.612%), imminent miscarriage (B = 3.084) with (χ2df1 = 13.581, p<0.0001) (95% CI: 4.237-112.668%), vulvovaginitis during pregnancy (B = 3.525) with (χ2df1 = 10.063, p<0.002) (95% CI: 3.846-299.735%), as well as exacerbation of chronic pathology pre-existing pregnancy (B = 3.887) with (χ2df1 = 12.762, p<0.0001) (95% CI: 5.779-411.077%), supplemented with the age of the woman older than 30 years (B = 1.026), (χ2df1 = 4.388, p<0.036) (95% CI: 1.068-7.281%) and pregnancy-associated inflammatory pathologies of the respiratory system (B = 1.512) with (χ2df1 = 10.953, p<0.001) (95% CI: 1.852-11.098%).

Stability analysis by resampling the proposed model for determining the probability of premature birth using the bootstrapping method (1000 samples) showed that the coefficient is stable, significant and the sign remains unchanged, which means that potential predictors identified from this model remain stable.

The area under the curve (AUC) ROC, for the predictive model, was 0.914, the informativeness of the test being considered excellent, with a 95% confidence interval (0.865, 0.963) and with a significant difference from the value of 0.5 (p < 0.001) (figure 8).

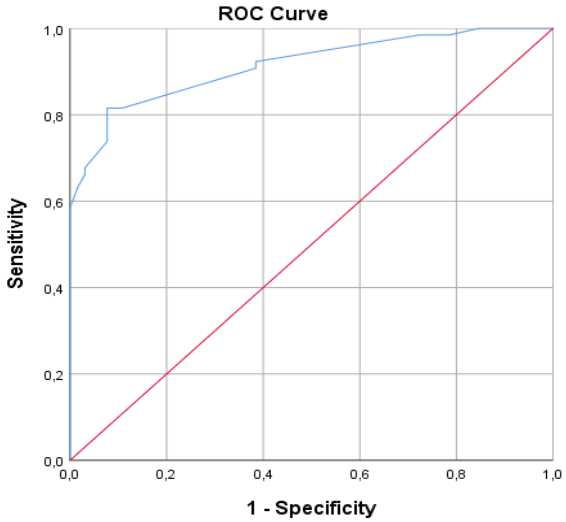


Figure 8. **ROC curve for estimating the probability of premature birth of the Clinical Predictive Model 2**

Therefore, the developed model has the ability to predict premature birth, having 6 predictors as follows. The age of the woman over 30 years old is a significant indicator for premature birth with OR=2.789 (95%CI 1.068, 7.281); the presence of infectious-inflammatory pathology of the respiratory system increases the probability of premature birth with OR=4.534 (95%CI 1.852, 11.098); Iron deficiency anemia is a predictor that increases the probability of premature birth with OR=0.12 (95%CI 0.23, 0.612); and imminent miscarriage increases the probability of premature birth with OR=21.849 (95%CI 4.237, 112.668). Another predictor – vulvovaginitis during

pregnancy increases the probability of premature birth with OR=33.952 (95%CI 3.846, 299.735), the last predictor being the exacerbation of chronic pathology pre-existing pregnancy with OR = 48.740 95%CI 5.779, 411.077.

The developed clinical predictive model 3 enrolled as covariates the inflammatory-infectious pathologies associated with pregnancy, such as the respiratory system, the genital tract and the renal system, additionally including the variable of the age of the pregnant woman over 30 years. This developed model demonstrated the ability to predict premature birth, the null hypothesis being rejected (Omnibus Test of Model Coefficients (χ2df =56.076, p<0.001).

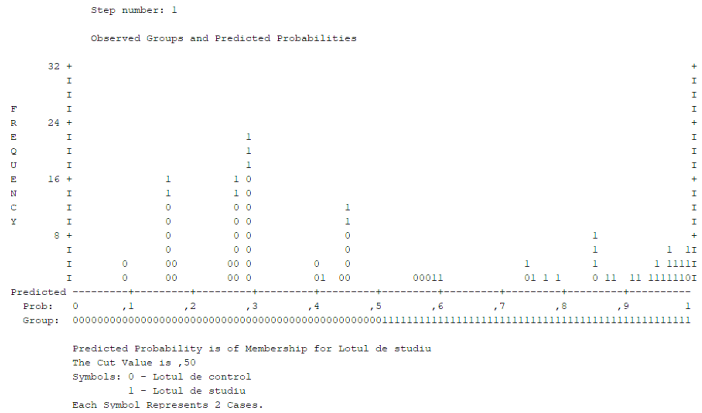


Figure 9. **Preterm birth probability classification chart for Clinical Predictive Model 3**

Further analysis revealed the following characteristics of the validated model. The determination indicator, Nagelkerke R Square, showed the value 0.467 (46.7%), which shows us that 46.7% of the dispersion of interest (preterm birth) was explained/covered by the covariates in the proposed clinical predictive model. The calibration indicator (Hosmer–Lemeshow test) demonstrated a non-significant value, χ2df7=10.636, p=0.155 – an indicator of sufficient calibration, the data being faithful in the sense of the precision of the results obtained over the entire amplitude of the predicted scores with the ability to stratify patients according to the studied risks within the highlighted groups. The discrimination indicators in the classification table, namely specificity and sensitivity, were equal to 67.7% and 90.8%, respectively, the summary (global) percentage was estimated at 79.2%. The results were obtained at the critical point value of 0.5 (figure 9).

The model included the basic constant (B=-3.062) of which: age older than 30 years (B=0.681) with (χ2df1=3.301, p=0.069) (95% CI:0.948-4.115), pregnancy-related inflammatory pathologies of the renal system (B=0.646) with (χ2df1=8.671, p=0.003) (95% CI:1.241-2.933), genital tract (B=1.308) with (χ2df1=9.275, p=0.002) (95% CI:1.594-8.578), and respiratory system (B=1.436) with (χ2df1=12.115, p=0.001) (95% CI:1.873-9.436). Stability analysis by resampling the proposed model for determining the probability of premature birth using the bootstrapping method

(1000 samples) showed that the coefficient is stable, significant and the sign in front remains unchanged.

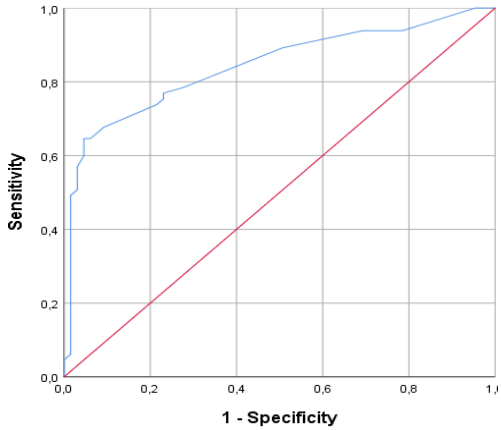


Figure 10. **ROC curve for estimating the probability of premature birth of the Clinical Predictive Model 3**

The area under the ROC curve, for the predictive model, was 0.842, the informativeness of the test being very good, with 95%CI (0.771, 0.912) and with a significant difference from the value of 0.5 ($p < 0.001$) (figure 10).

Therefore, the developed model has the ability to predict premature birth, having 4 predictors as follows: pregnant woman's age over 30 years - the older the woman, the higher the probability of premature birth with OR=1.975 (95%CI 0.948, 4.115), the existence of inflammatory pathologies of the renal system, genital tract and respiratory system, respectively, will increase the probability of premature birth with OR=1.908 (95%CI 1.241, 2.933), OR=3.698 (95%CI 1.594, 8.578) and OR=4.204 (95%CI 1.873, 9.436).

5.2. Comparative evaluation of predictive models for preterm birth

In the research process, based on the study objectives and the results obtained, a comparative analysis of the obtained predictive models was carried out to identify which of these three presented higher significant values (table 5).

Therefore, it was established that the *Clinical Predictive Model 1* compared to the *Clinical Predictive Model 2* demonstrated its inferiority through a lower coefficient of determination (55.3% vs 66.8%), the calibration being adequate in the case of both models: the *clinical predictive model 1* (χ2df4=0.864, p=0.930) compared to the *Clinical Predictive Model 2* (χ2df6=2.102, p = 0.910). Moreover, a significant difference in the values of the area under the ROC curve (z=-2.948, p=0.003) was also determined, being more extensive for the clinical predictive model 2 - an indicator that determines that this model presents a better discriminative ability compared to the *Clinical Predictive Model 1*.

The comparative analysis of *Clinical Predictive Model 1*, compared to *Clinical Predictive Model 3*, showed a higher coefficient of determination (55.3% vs 46.7%),

being well calibrated (χ2df4=0.864, p = 0.930) and with similar areas under the ROC curve (z = 0.247, p = 0.805). The results obtained reported that the *Clinical Predictive Model 3* has inferior characteristics compared to the *Clinical Predictive Model 1*.

Table 5. **Comparative evaluation of ROC curves for the developed models**

Test Result Pair(s)	Asymptotic		AUC Difference	Std. Error Difference[b]	Asymptotic 95% Confidence Interval	
	z	Sig. (2-tail)[a]			Lower Bound	Upper Bound
Model 1 – Model 2	-2,948	0,003	-0,062	0,231	-0,103	-0,021
Model 1 - Model 3	,247	0,805	0,010	0,255	-0,071	0,092
Model 2 - Model 3	2,375	0,018	0,072	0,243	0,013	0,132

Analyzing the *Clinical Predictive Model 2* which included more comorbidities, as well as the patient's age variable, compared to the *Clinical Predictive Model 3*, we obtained a maximum coefficient of determination of 66.8% for the *Clinical Predictive Model 2*, being well calibrated (χ2df6=2.102, p = 0.910) and significantly higher according to the value of the area under the ROC curve (z=2.375, p=0.018) compared to the *Clinical Predictive Model 3* which presented a lower coefficient of determination of 46.7%. Based on the results obtained, it was established that *Clinical Predictive Model 2* presented significantly higher values compared to *Clinical Predictive Model 1* (z = -2.948, p = 0.003) and *Clinical Predictive Model 3* (z = 2.375, p = 0.018), with areas under the ROC curve of *Clinical Predictive Model 1* and *Clinical Predictive Model 3* similar (z = 0.247, p = 0.805) compared to that of Clinical Predictive Model 2 (z = -2.948, p = 0.003), which being more extensive determined a superior indicator to the other models and this model presents a better discriminative ability compared to the other models developed.

5.3 Development of the algorithm for the prediction of premature birth

In accordance with the results of our own study, the Algorithm for the management of pregnant women at risk of spontaneous preterm birth was developed. Applying an algorithm for identifying pregnant women at risk of spontaneous preterm birth allows for the application of early interventions and personalized management strategies, facilitating therapeutic interventions that lead to improved maternal-fetal outcomes.

Thus, the developed Algorithm for the management of pregnant women at risk of spontaneous preterm birth is structured in three essential stages, each contributing to the targeted identification and triage of pregnant women at risk of preterm birth.

Stage I: Initial identification of pregnant women at potential risk of preterm birth. Therefore, for the initial identification (at the first prenatal visit) of pregnant women at

risk of preterm birth, the *Clinical Predictive Model 2* of Preterm Birth will be applied, which was developed within the current research and which presented significantly higher values compared to the other predictive models developed. Thus, a thorough assessment of the medical and obstetric history, including age, obstetric history and existing comorbidities, will be performed. A scoring system will be applied, in which each covariate in the *Clinical Predictive Model* will receive an appropriate score:

- age over 30 years: 0-1 points;
- low serum Hg value<11 g/dl: 0-1 points;
- presence of inflammatory pathology of the respiratory system associated with pregnancy: 0-1 points;
- exacerbation of chronic infectious pathology associated with pregnancy: 0-1 points;
- imminent miscarriage: 0-1 points;
- presence of vulvovaginitis in the current pregnancy: 0-1 points.

The total score will be obtained by summing the points for each covariate, with a maximum total score of 6 points, thus determining the level of risk for each pregnant woman, allowing a preliminary classification according to the score obtained.
The scores will be interpreted and classified as follows:

- 0-1 point: low risk;
- 2-6 points: high risk.

Stage II: Determination of serum values of polyfunctional immunomodulatory proteins. Pregnant women who will be included in the high-risk group will benefit from additional paraclinical evaluation that will include the assessment of serum values of polyfunctional immunomodulatory proteins such as Lactoferrin and α2-Macroglobulin.

Stage III: Classification of pregnant women according to the assessed risk. Pregnant women with serum values of LF < 0.99 U/ml and α2-MG > 41.91 pg/ml will be included in the high-risk group for premature birth and will be subject to an individualized clinical evaluation and intervention protocol.

The proposed management for these pregnant women includes:

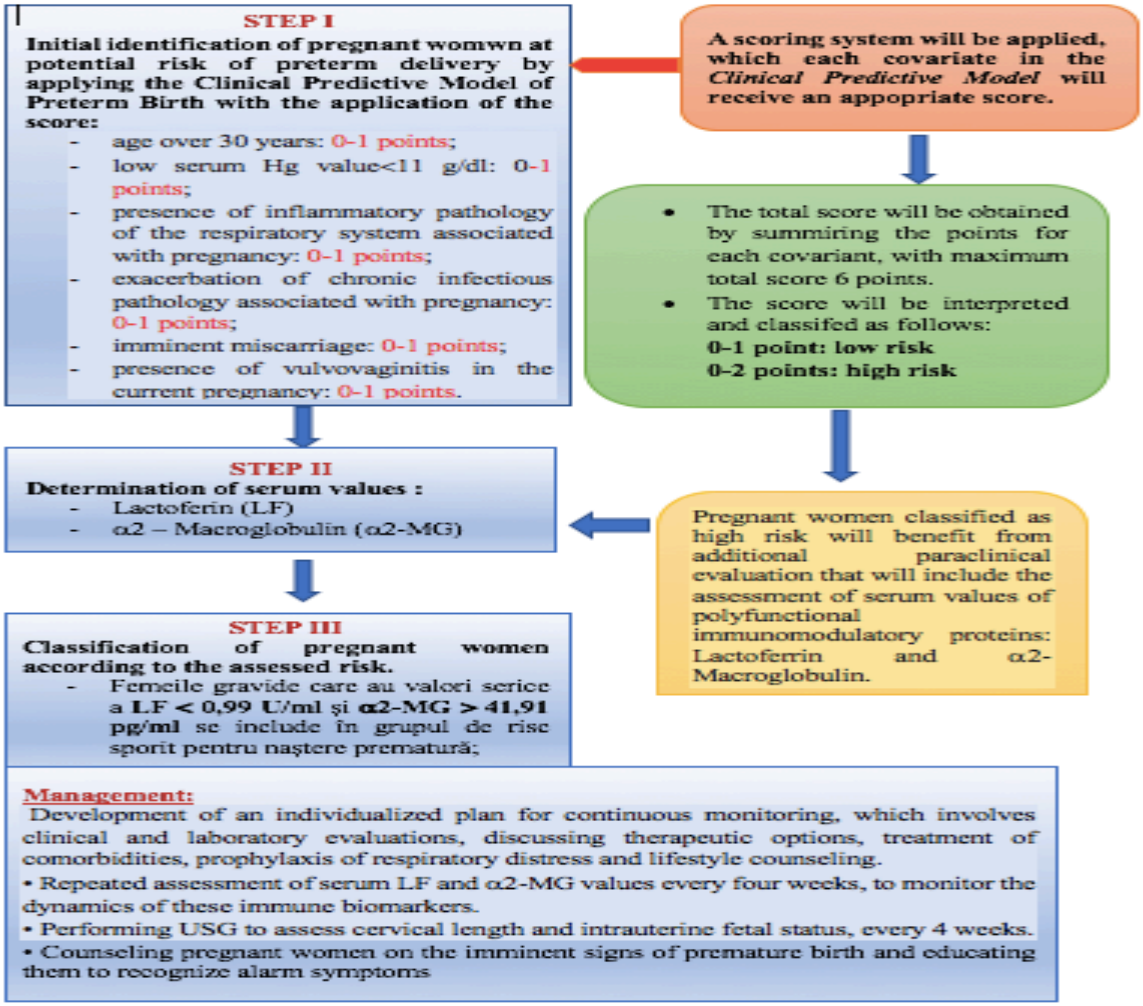
• Development of an individualized plan for continuous monitoring, which involves clinical and laboratory evaluations, discussing therapeutic options, treatment of comorbidities, prophylaxis of respiratory distress and lifestyle counseling.

• Repeated assessment of serum LF and α2-MG values every four weeks, to monitor the dynamics of these immune biomarkers.

• Performing USG to assess cervical length and intrauterine fetal status, every 4 weeks.

• Counseling pregnant women on the imminent signs of premature birth and educating them to recognize alarm symptoms.

Algorithm for the management of pregnant women at risk of spontaneous preterm birth



CONCLUSIONS

The results of the study allowed us to formulate the following conclusions:

1. The study of the anamnestic features and the evolution of pregnancy in women who gave birth prematurely established the presence of psychoemotional overstrain at work ($\chi^2$1df =4.795, p=0.029), a high frequency of imminent premature birth in the anamnesis ($\chi^2$1df = 18.246, p=0.0001) and premature birth in the anamnesis ($\chi^2$1df = 23.269, p=0.0001), pre-existing nephrourinary tract disorders before pregnancy ($\chi^2$1df 22.031, p=0.0001), a high rate of iron deficiency anemia ($\chi^2$2df 7.488, p=0.024), imminent spontaneous abortion ($\chi^2$1df = 22.031, p=0.0001), imminent premature birth in the current pregnancy ($\chi^2$1df=23.269, p=0.0001), of infectious-inflammatory pathology in the II and III trimesters of pregnancy: (respiratory (χ^2=18.667, p=0.001), nephrourinary

(χ^2=9.290, p=0.026), genital tract (χ^2=16.321, p=0.001)), compared to the control group.

2. The low serum levels of Lactoferrin (LF) in patients with preterm birth, compared to respondents who gave birth at term (rrank biserial=0.98, 95%CI 0.97, 0.99; p<0.001), confirm the protective role of this protein in maintaining immunological balance and preventing intrauterine inflammation. The significantly reduced value of LF in the preterm group suggests that the deficiency of this biomarker is an alarm signal for premature initiation of labor. At the same time, the increased serum levels of α2-Macroglobulin (α2-MG) in women with preterm birth (rbiserial=0.97, 95%CI -0.98, -0.96; p<0.001), indicate an excessive activation of the inflammatory response, which may accelerate cervical maturation and the initiation of uterine contractions.
3. The study found that the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α were significantly higher in patients with preterm birth compared to term birth ((IL-1β ($r_{rank\ biserial}$=0.84, 95%CI -0.89, -0.77; p<0.001), Il-6 ($r_{rank\ biserial}$=0.85, 95%CI -0.89, -0.78; p<0.001) and TNF-α ($r_{rank\ biserial}$=0.78, 95%CI -0.85, -0.69; p<0.001)), which confirms the importance of maternal systemic inflammation in premature labor initiation. Complementary cytokines IL-6 (μ_{median}=144.06 pg/ml; μ_{median}=52.11 pg/ml; μ_{median}=124.73 pg/ml; μ_{median}=124.73 pg/ml; p<0.001) and TNF-α (μ_{median}=71.55 pg/ml; μ_{median}=25.77 pg/ml; μ_{median}=60.28 pg/ml; p<0.001) showed strong correlations with the severity of prematurity, reinforcing the role of these cytokines as possible predictive biomarkers for this obstetric complication.
4. Correlation analysis between immunomodulatory biomarkers and pro-inflammatory cytokines, in the study group demonstrated an inverse relationship between LF and the cytokines IL-1β, IL-6, TNF-α ((LF and IL-1β (rs=-0.396 95%CI -0.608, -0.133; p=0.001); LF and IL-6 (rs=-0.377 95%CI -0.580, -0.148; p=0.002); LF and TNF-α (rs=-0.450 95%CI -0.654, -0.212; p<0.002, Pearson correlation being inverse)), but a positive correlation between α2-MG and IL-1β (rs=0.289 95%CI 0.028, 0.525; p=0.019), α2-MG and IL-6 (rs=0.609 95%CI 0.406, 0.757; p<0.001, α2-MG and TNF-α (rs=0.522 95%CI 0.291, 0.693; p<0.001, Pearson correlation being direct, which suggests a strong immunological imbalance in patients with preterm birth. High values of α2-MG and pro-inflammatory cytokines could be used to establish treatment strategies, including the administration of anti-inflammatory therapies and antenatal corticosteroids to prevent preterm birth.
5. As a result of the research, three predictive models were developed that demonstrated the ability to predict the probability of preterm birth, with a

rejected null hypothesis: Clinical predictive model 1, determination indicator, Nagelkerke R Square at a value of 0.533 (55.3%), Clinical predictive model 2, determination indicator, Nagelkerke R Square at a value of 0.668 (66.8%) and Clinical predictive model 3, with determination indicator, Nagelkerke R Square of 0.467 (46.7%). Comparative evaluation of the developed models demonstrated superior characteristics of Clinical predictive model 2 compared to the other models (z=-2.948, p=0.003). The use of this predictive model in clinical practice allows the identification of pregnant women at increased risk of preterm labor, with their subsequent inclusion in the "Algorithm for the management of pregnant women at risk of spontaneous preterm birth", developed based on the study, which could optimize the management of high-risk pregnancies, allowing for earlier and more effective medical intervention.

6. The results obtained confirm that premature birth is a complex phenomenon, determined by socio-anamnesis and pathological conditions, and the risk factors identified in the study highlighted the importance of the obstetric history and health status of the pregnant woman on the evolution of pregnancy and perinatal prognosis. Early identification of pregnant women at risk, by evaluating the obstetric history and medical history, would allow the application of personalized prevention strategies, which could reduce the incidence of premature birth.
7. The data obtained validate the hypothesis that decreased serum LF values and increased α2-MG values act as an amplifier of inflammation, contributing to the onset of preterm labor, and the integration of LF and α2-MG testing into prenatal screening could lead to better obstetric risk stratification, allowing for personalized preventive interventions.

PRACTICAL RECOMMENDATIONS

Based on the results obtained and the risk factors identified for preterm birth, the following clinical recommendations are proposed to optimize the surveillance of pregnant women and prevent prematurity in obstetric practice:

1. Ensuring early screening of patients at high risk of prematurity, by identifying obstetric history, history of spontaneous abortions, previous preterm births, associated pathologies, monitoring maternal age and sociodemographic factors. Evaluation of general health status, pre-existing conditions, especially urinary, respiratory, vaginal infections, iron deficiency anemia and renal pathologies - pathologies that significantly increase the risk of prematurity.
2. Intensive surveillance of patients with a history of prematurity, especially pregnant women who have had a previous premature birth, with the

development of an individualized antenatal care plan, the inclusion of these women in special pregnancy monitoring programs, with rigorous examinations, more frequent ultrasound assessments and clinical conduct in multidisciplinary collaboration of obstetricians, neonatologists, nutritionists and psychologists.

3. Detection and treatment of maternal infections by performing vaginal and urinary bacteriological screening, testing for viral and bacterial infections in high-risk patients, early treatment of infections, which can reduce the incidence of intrauterine inflammation and, implicitly, prematurity.
4. Implementation of immunological screening to identify pregnant women at high risk of prematurity, by integrating Lactoferrin (LF) and α2-Macroglobulin (α2-MG) testing into prenatal screening, along with clinical and ultrasound factors, to allow for a more precise stratification of high-risk patients.
5. Given that elevated values of immunological biomarkers are important predictors of premature labor initiation, it is welcome to ensure monitoring of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) in patients with obstetric risk factors, combined with ultrasound screening of cervical length, which could increase the accuracy of prematurity diagnosis.
6. Optimizing the clinical management of pregnant women at risk of prematurity, through intensive monitoring of patients with abnormal serum values of LF, α2-MG, IL-1β, IL-6 and TNF-α with their inclusion in a frequent medical surveillance program, with regular ultrasound checks and periodic serological evaluations that would allow early identification of patients at risk and the application of effective preventive measures.
7. Developing a predictive model for the management of high-risk pregnancies, by using a combined model for the assessment of prematurity, which would include obstetric history, ultrasound data and immunological factors (LF, α2-MG, IL-1β, IL-6 and TNF-α) would allow personalization of medical conduct for high-risk patients, who will benefit from early prophylactic treatment and intensive monitoring, thus reducing the number of unnecessary obstetric interventions and more efficient allocation of medical resources.

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