Doctoral School in Medical Sciences

VERA OLEINIC

PREECLAMPSIA AND THE ROLE OF PREDICTION FACTORS IN THE THIRD TRIMESTER OF PREGNANCY

321.15 - OBSTETRICS AND GYNECOLOGY

Summary of the doctoral thesis in medical sciences

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The thesis was elaborated within the Department of Obstetrics and Gynecology, Obstetrics, Gynecology and Human Reproduction Discipline, Nicolae Testemitanu State University of Medicine and Pharmacy.

Scientific advisor:
Friptu Valentin
hab. dr. in med. science, univ. prof.   _____

Members of the guidance committee:
Bologan Ion
dr. in med. science, associate prof.   _____
Mihalcean Luminița
dr. in med. science, associate prof.   _____
Ostrofeț Constantin
dr. in med. science, associate prof.   _____

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The Committee Members for the Public Defense:

The President:

Cernețchi Olga
hab. dr. in med. science, univ. prof.   _____

Members:
Friptul Valentin
hab. dr. in med. science, univ. prof.   _____
Sofroni Dumitru
hab. dr. in med. science, univ. prof   _____
Iliadi-Tulbure Corina
dr. in med. science, associate prof.   _____
Marian-Pavlenco Angela
dr. in med. science, associate prof.   _____

Author

Oleinic Vera   _____

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SUMMARY

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LIST OF ABBREVIATIONS

ALAT   alanine aminotransferase
ASAT   aspartate aminotransferase
IVF   in vitro fertilization
HTN   hypertension
HIF   hypoxia-inducible factor
IL-6   interleukin 6
BMI   body mass index
LDH   lactate dehydrogenase
PE   preeclampsia
PI   pulsatile index
IUGR   intrauterine growth restriction
RI   resistance index
S/D   systole/diastole ratio
USG   ultrasonography.

INTRODUCTION

Actuality and importance of the topic addressed. Preeclampsia (PE) remains a current problem in contemporary obstetrics and can complicate 2-8% of all pregnancies, is a major cause of maternal and perinatal morbidity and mortality worldwide, and also poses long-term maternal risks of developing hypertension, ischemic heart disease, stroke and venous thromboembolism [6, 10, 13].

Several studies have looked at risk factors for preeclampsia, which are: older maternal age, black women, and maternal obesity. Age > 35 years has repeatedly been shown to be associated with an approximately 2-fold increased risk for postpartum preeclampsia, an increased risk of up to 7-fold is associated with increased body mass index > 40 kg/m2 [5, 6].

Increasing body mass index (BMI) is positively associated with an increased risk of PE. Women with a pre-pregnancy BMI of 35 kg/m2 or more have a 30% higher risk of developing PE [6, 8].

The exact pathological mechanisms that result in the development of PE are unknown, and PE is more of a syndrome with different subtypes than a single disease. The pathogenesis is multifactorial, resulting from an interaction of genetic, environmental and abnormal placentation. The genetic etiology of PE is evident by the increased risk of the disease in patients with a family history of PE, with current epidemiological evidence of both maternal and paternal origin, and the influence of the environment is evident by the contribution of the socio-economic status of the organism. weight, parity. Arterial hypertension can be considered an adaptive response of the damaged placenta, which signals to the mother the need to maintain perfusion, this is achieved by increasing maternal cardiac output [7, 12, 14].

PE is considered to be a two-step disease, with the first step occurring in early pregnancy and characterized by abnormal trophoblast invasion and remodeling of the uterine spiral arteries and abnormal placentation, in turn leading to an abnormal maternal vascular response resulting in a imbalance of angiogenic and antiangiogenic factors, a maternal immune and inflammatory response, increased vascular resistance, activation of the coagulation system and endothelial dysfunction [15, 18].

In the past decade, two screening tests have been developed that have been integrated into clinical care. The first is a first-trimester screening test that identifies people at risk of developing premature PE. The second is designed for the second and third trimesters of pregnancy. There are several guidelines for risk stratification using maternal risk factors [1, 16, 17]. Currently, the prediction of PE is based on screening pregnant women using checklists of clinical factors, or biochemical and biophysical tests in the first half of pregnancy. The ideal test to identify women who will develop preeclampsia should be simple, rapid and easy to perform, non-invasive, affordable, easily accessible, applicable in early pregnancy, cause minimal discomfort or risk, and be valid, reliable and reproducible, with high sensitivity and specificity [2, 3, 9].

In this context, identifying the most accurate methods of predicting PE and performing adequate prophylaxis remains the main task in obstetrics. A combination of personal maternal risk factors, the Doppler performance of the uterine arteries, in

association with the performance of specific biomarkers for PE, may give us greater accuracy in the early detection of pregnant women at risk of developing PE[3, 4, 18].

The completed thesis comes with a solution to optimize management in PE, to prevent severe complications. Identification of personal maternal risk factors, clinical and biochemical parameters that may be involved in the etiopathogenesis of PE, the mechanisms underlying the development of this condition and the identification of therapeutic solutions that could be implemented in clinical practice to improve the prognosis of preeclampsia. The research carried out analyzed the etiological factors, as well as the effective methods of predicting PE, in order to be able to apply prophylactic measures as early as possible. PE prediction methods are the basis for improving the prognosis of PE. Thus, following the results obtained from the conducted study, we can confirm that HIF-1a, IL-6 and uterine artery Doppler indices can be considered relevant markers to predict PE and can be recommended for use in practice.

The purpose of the study. Evaluation of the role of predictors of PE in the third trimester of pregnancy, to optimize management and improve maternal-fetal prognosis.

Objectives of the study:
1. Establishing the anamnestic and evolutionary characteristics of pregnancy in pregnant women with PE in the third trimester of pregnancy.
2. Evaluation of the risk factors that contribute to the occurrence of PE in the third trimester of pregnancy.
3. Evaluation of the level of HIF-1a, IL-6, Doppler indices of the uterine arteries and establishing their interrelation in the prediction of PE.
4. Establishing the behavioral algorithm for pregnant women at risk of developing PE.

General research methodology. The research was carried out at the Department of Obstetrics and Gynecology within USMF,,Nicolae Testemițanu", IMSP SCM,,Gheorghe Paladi", AMT Buiucani and the Biochemistry Laboratory of IP USMF "Nicolae Testemițanu" during 2018 - 2023 and offers all research stages. The research was positively approved by the Research Ethics Committee of the "Nicolae Testemițanu" State University of Medicine and Pharmacy (no. 22 of 08/04/2019).

The thesis topic was approved at the meeting of the Department of Obstetrics, Gynecology and Human Reproduction (no. 8 of 21.01.2019) and in the record of the Scientific Seminar of Profile 321.15 – Obstetrics and Gynecology (no. 3 of 16.04.2019).

The results of the study were discussed and approved at the meeting of the Discipline of Obstetrics, Gynecology and Human Reproduction (no. 8 of 29.02.2024) and in the record of the Scientific Seminar of Profile 321.15 – Obstetrics and Gynecology (no. 11 of 17.04.2404).

Scientific novelty of the results obtained. By analyzing in detail the personal and medical risk factors associated with PE, as well as the evolution of pregnancy, the research contributed to understanding the complexity of this condition. This approach allowed us to identify risk factors, and demonstrated the role of biomarkers HIF-1a, IL-6 and their interrelation with Doppler indices of uterine arteries in predicting PE. The implementation of the behavioral algorithm for predicting PE represents a contribution to medical practice, in order to prevent the occurrence of severe maternal-fetal complications.

The scientific problem solved in the thesis consists in determining the role of biomarkers HIF-1a, IL-6 and Doppler indices of uterine arteries in the development of PE, and the results of this research confirm the relevance of the study.

Theoretical significance of the work. The results of the study expand the theoretical basis for the use of biomarkers in predicting PE. Threshold levels for HIF-1a (>320,65 pg/ml) and IL-6 (>15.08 pg/ml) were established, which together with altered uterine artery Doppler parameters (PI) are associated with an increased risk of PE. Based on the results received, a behavioral algorithm for predicting PE in the third trimester of pregnancy was developed.

Applicative value of the work. The application of the proposed algorithm, which consists of identifying maternal risk factors, elevated serum levels of HIF-1a (>320.65 pg/ml) and IL-6 (>15.08 pg/ml), pathological Doppler velocimetry index (PI), allows us to identify pregnant women at risk of developing PE. Thus, the performance of these biomarkers is necessary for the prediction of PE in the third trimester of pregnancy. The results obtained provide us with extensive theoretical information that can be used in practice to optimize the management of pregnant women with PE.

Approval of scientific results. The results were presented and discussed at the Congress dedicated to the 75th anniversary of the establishment of the USMF "Nicolae Testemițanu" (Chisinau 2020), the Hospital Days Conference "Elena Doamna" (Iași 2023), the Annual Scientific Conference (Chisinau 2023).

The volume and structure of the thesis. The work is presented on 150 pages with the following structure: table of contents, annotation, list of abbreviations, introduction, bibliographic analysis on the topic of the thesis, research materials and methods, own results presented in 3 chapters, synthesis of the obtained results. , general conclusions, bibliography comprising 120 national and international sources, 45 figures, 6 tables, 90 appendices. The results of own research are presented in 9 scientific papers and presented at 3 national and international conferences.

Key words: preeclampsia, predictive markers, third trimester, ultrasound Doppler.

THESIS CONTENT

1. THE ROLE OF BIOMARKERS IN THE PREVENTION OF PREECLAMPSIA

This chapter of the thesis included a synthesis of data from the national and international literature, which includes the most recent studies in the field of obstetrics-gynecology that study the problem of PE and the complications induced by this condition. According to literature data, PE remains one of the main problems in contemporary obstetrics, being the major cause of maternal-fetal morbidity and mortality, and the etiological mechanism is multifactorial. However, the main task of specialists in the field is to predict PE and identify the most effective method that can be applied, and this method must be safe, harmless to pregnant women, cost-effective and with increased specificity and sensitivity, so that prophylaxis is indicated as early as possible and careful monitoring of pregnant women with risk factors. The identification of personal risk factors in combination with the performance of biomarkers and ultrasonographic markers are increasingly described in the international literature as an effective method to predict the occurrence of PE and determine the severity of the disease.

2. MATERIALS AND RESEARCH METHODS

In order to achieve the purpose of the research and the proposed objectives, a cohort study was carried out, carried out in two phases, which included the retrospective and prospective study. The research was carried out at the Department of Obstetrics and Gynecology, the Discipline of Obstetrics, Gynecology and Human Reproduction within USMF,,,Nicolae Testemițanu", IMSP SCM,,Gheorghe Paladi", AMT Buiucani and the Biochemistry Laboratory of IP USMF "Nicolae Testemițanu " during the period 2018 - 2023 and provides for all stages of the research:
 1) developing the study plan, determining the sample;
 2) accumulation of research material;
 3) statistical material processing;
 4) analyzing the results obtained and drawing up conclusions.

The research was positively approved by the Research Ethics Committee of the "Nicolae Testemițanu" State University of Medicine and Pharmacy (no. 22 of 08/04/2019).

The current scientific medical literature was analyzed with the description of the relevant points in the Literature Review. Based on information collected from various sources such as articles, multicenter studies, and online sources of scientific literature, statistical incidence data from different countries regarding risk, etiologic, and predictive factors for PE were elucidated.

The aim and objectives of the research were established and the design for the retrospective descriptive analytic and prospective observational cohort studies was developed.

Phase I - retrospective study, a descriptive study was carried out (n-128), cases with non-severe preeclampsia (PEN) and severe preeclampsia (PES) selected from the archive of IMSP CSM "Gheorghe Paladi", from the period 2018-2020.

In this stage, the clinical, anamnestic aspects and the evolution of pregnancy in pregnant women with PE were elucidated. The necessary data were collected from the observation sheets of the pregnant women, based on the questionnaire specially developed for the research. The risk factors present in the anamnesis of pregnant women with PE, the evolution of the current pregnancy and the particularities of pregnancy in these pregnant women were analyzed. These data were needed to confirm the actuality of PE and to analyze predictive factors.

Phase II - the prospective study, in which pregnant women in the third trimester of pregnancy were included, the study group included pregnant women who were treated in the pregnancy pathology departments of IMSP SCM "Gheorghe Paladi" or who were urgently hospitalized due to hypertension arterial, associated with symptoms characteristic of PE, and the control group included pregnant women who went to the doctor for a routine check-up in the third trimester of pregnancy in AMT Buiucani, the term of pregnancy of the pregnant women included in the study was carried out between 29+0 - 39+6 w.p., in the period 2020 - 2023.

The L1 research group was selected based on the following study inclusion criteria: Third trimester pregnant women with PE; Age of pregnant women > 18 years; Consent of the woman to participate in the study. Exclusion criteria from the study: Age of pregnant women < 18 years; Pregnant women in the first and second trimester of pregnancy; Pregnant women with essential hypertension, HELLP syndrome; Lack of consent to participate in the study. The L0 control group consisted of 48 pregnant women selected based on the following criteria for inclusion in the study: Age of pregnant women > 18 years; Pregnant women in the third trimester of physiological pregnancy; Consent of the pregnant woman to participate in the study. Exclusion criteria from the study: Age of pregnant women < 18 years; Pregnant women in the first and second trimester of pregnancy; Pregnant women with essential hypertension, gestational hypertension, HELLP syndrome; Lack of consent to participate in the study.

The following data collection methods were applied: analytical method, comparison method, statistical observation method and mathematical method. The analytical method was applied to study the role of biomarkers in the prediction and diagnosis of PE. The statistical observation method studied the role of HIF-1α, IL-6 and Doppler indices on uterine arteries. Data were collected by: investigating and extracting information from medical records. The statistical method was used to process the obtained information. Collected data were processed through RStudio software (rstudio-com.netlify.app) and IBM SPSS Statistics version 26.

3. CLINICAL CHARACTERISTICS, HISTORY AND EVOLUTION IN PREGNANT WOMEN WITH PREECLAMPSIA

3.1. Establishing the clinical-evolutionary characteristics of pregnancy in pregnant women with preeclampsia in the third trimester of pregnancy

To achieve the proposed goal, a retrospective, descriptive study was carried out, carried out in the period 2018-2020, in which 128 pregnant women were included, divided into two groups: pregnant women with PES and PEN, from the IMSP CSM

"Gheorghe Paladi ". In order to establish the role of risk factors from the anamnesis of the pregnant women and the evolution of the current pregnancy, the medical records of the pregnant women were studied to determine the relevant obstetric characteristics.

Pregnant women who develop PE may frequently have a history of spontaneous abortions - 45 (35.2%), with predominance in the group with PES - 32 (50.0%) versus PEN - 13 (20.3%), blocked pregnancies - 38 (29.7%)), with a prevalence of cases in the group with PES - 26 (40.6%) compared to the group with PEN - 12 (18.8%) and the presence of CVS pathology - in the group of pregnant women with PES were recorded more frequently, namely in 23 (35.9%) cases, and in the group with PEN 13 (20.3%) pregnant women reported CVS disorders. Pregnant women with an increased pre-pregnancy BMI have a higher risk of developing PES compared to PEN (p=0.005).

The presence of gestational hypertension in pregnant women can be complicated with PE during pregnancy, thus, 85 (66.4%) of the total number of pregnant women who were monitored with gestational hypertension later developed PE (p<0.001), especially PES 55 (85.9%).

The rate of cesarean operations caused by PE is increasing, from the total number of pregnant women in 99 (77.3%) cases the pregnancy was terminated by CO.

After analyzing the data obtained from the retrospective study, we can establish that pregnant women with a history of risk factors, such as spontaneous abortions and blocked pregnancies, have a higher risk of developing PE and especially severe PE. Increasing BMI in women is also one of the major risk factors for pre-eclampsia, and with obesity increasing in the whole population and especially in women, this could lead to an increase in the number of cases of PE. PE in the future, especially PES, which can lead to serious consequences for the health of the mother and the fetus. And with the increase in the number of PES cases, the number of girls affected by IUGR and prematurity also increases, and the number of caesarean sections increases. Thus, further studies are warranted to establish the most frequent risk factors for PE in pregnant women and to discover new biomarkers for predicting PE.

4. PROGNOSIS OF PREECLAMPSIA IN PREGNANT WOMEN WITH RISK FACTORS IN THE THIRD TRIMESTER OF PREGNANCY

4.1. Analysis of clinical-evolutionary characteristics in pregnant women with and without preeclampsia in the third trimester of pregnancy

In order to achieve the proposed goal, a prospective study was carried out, carried out in the period 2018-2023. The study included 96 pregnant women, who were divided into two groups: L1 - pregnant women who were diagnosed with PE (study group), L0 - pregnant women who did not present a diagnosis of PE (control group).

In the general analysis of the groups, the general characteristics of the pregnant women included in the study, obstetrical-gynecological anamnesis and somatics were described. By examining the anamnestic data of the pregnant women in both groups, we can select the patients who presented risk factors for PE, thus choosing the pregnant women who can later undergo laboratory and imaging screening for PE.

The most frequent signs and symptoms presented by pregnant women at the time of admission were: headache – 46.9% (95% CI 37.1, 56.8), epigastric pain – 18.8%

(95% CI 11.9, 27.4), nausea/vomiting – 6.3% (95% CI 2.7 , 12.4), visual disturbances – 10.4% (CI95% 5.5, 17.7) and the presence of pathological edema – 50.0% (CI95% 40.1, 59.9).

The age of the patients varied between 19 years and 39 years for L0, with an average of 30 years and a standard deviation of 5 years, and for L1 it ranged between 18 years and a maximum of 43 years, with an average of 30 years and a standard deviation of 7 years.

As described in the literature, obesity is associated with an increased risk of preeclampsia and gestational hypertension [4, 8]. The BMI of pregnant women in the group diagnosed with PE varied between a minimum of 18.6 and a maximum of 43.7. The mean of the L1 group was 26.3, with a standard deviation of 1.8. In the group of pregnant women without preeclampsia, the BMI was located in an interval with a minimum of 21.4 and a maximum of 30.2, the average BMI is located at approximately 23.3.

$W_{\text{Mann-Whitney}} = 1.7e{+}03, p = 1.73e{-}05, \hat{r}_{\text{biserial}}^{\text{rank}} = 0.51, CI_{95\%} [0.32, 0.66], n_{\text{obs}} = 96$
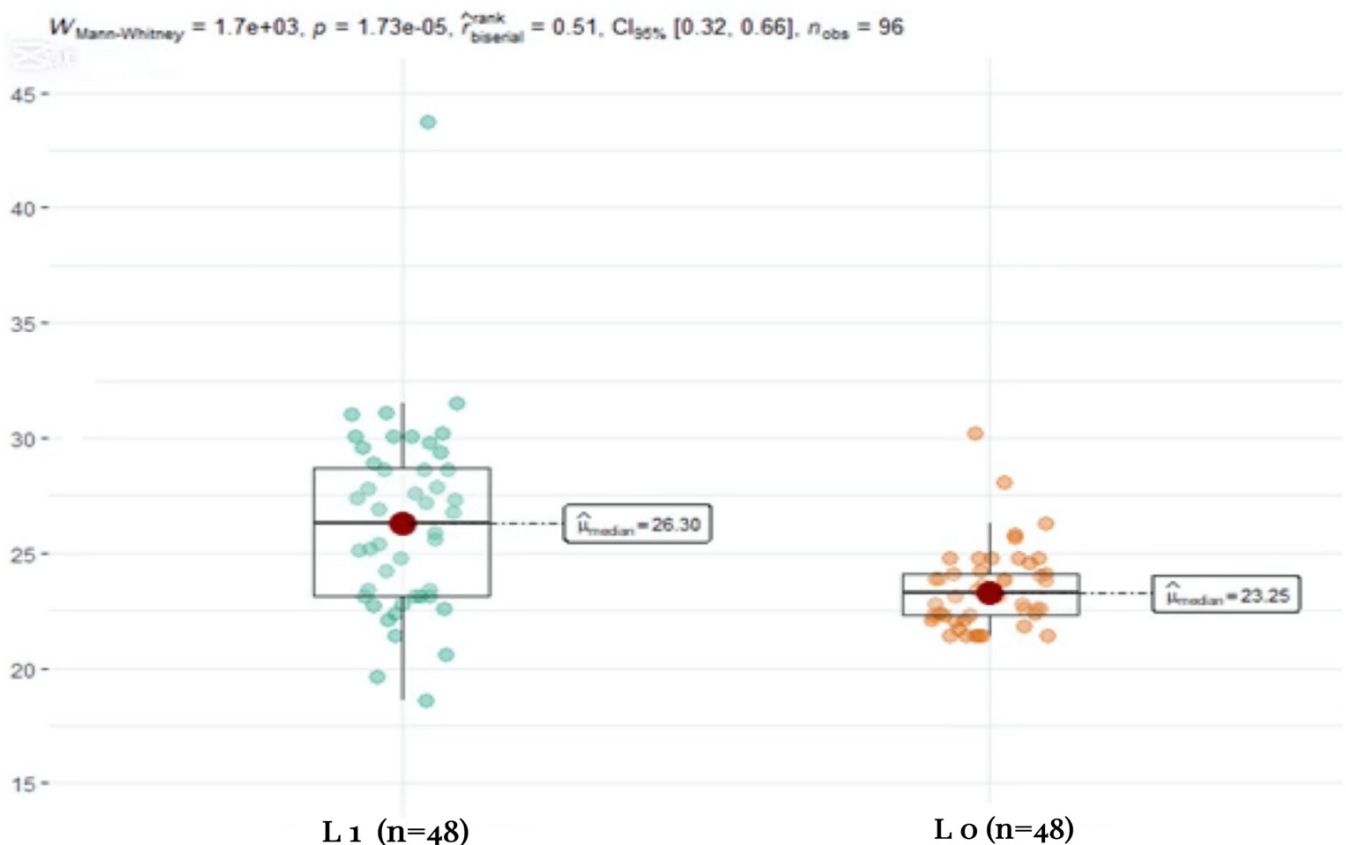
Note: * p < 0.001

Figure 1. **Comparative analysis of distribution by BMI in study groups**

The Mann-Whitney test was calculated to determine whether patients' increased BMI was associated with the risk of developing PE. From these data, it can be concluded that BMI was significantly higher in the group of pregnant women with PE

(U= 1738.5, p < 0.001) compared to the group of pregnant women without preeclampsia (figure 1).

It is well known in the literature that heart disease is a major risk factor for PE. Thus, we can observe that Cardiovascular diseases in the antecedents were suffered by approximately 2.1% (CI95% 0.2, 9.3) of pregnant women without PE and 27.1% (95% CI 16.1, 40.7) of pregnant women diagnosed with PE, observing a certain level of correlation between they.

In the Histogram in figure 2, an increased frequency of cases of cardiovascular system disorders in the antecedents is observed in the group of pregnant women diagnosed with PE.

The distribution of cardiovascular disease, was also demonstrated in this case by the values of the Pearson Chi square test, which, initially, was 12.04 (df = 1, p = 0.001), statistically significant, therefore we can conclude that the research groups differed in the chapter Antecedents of heart disease in the context of the onset of PE.

Pathological weight gain can be an early warning sign in the development of PE and serves as a reason for more thorough monitoring of the pregnant woman's condition. In the case of the patients included in the current research, only 16.7% (CI95% 8.2, 29.0) of the pregnant women in the group without PE, compared to 39.6% (CI95% 26.7, 53.7) of the pregnant women in the group with PE, had pathological weight gain, a predominance is observed of cases of weight gain in the group of pregnant women diagnosed with PE, (p = 0.013).
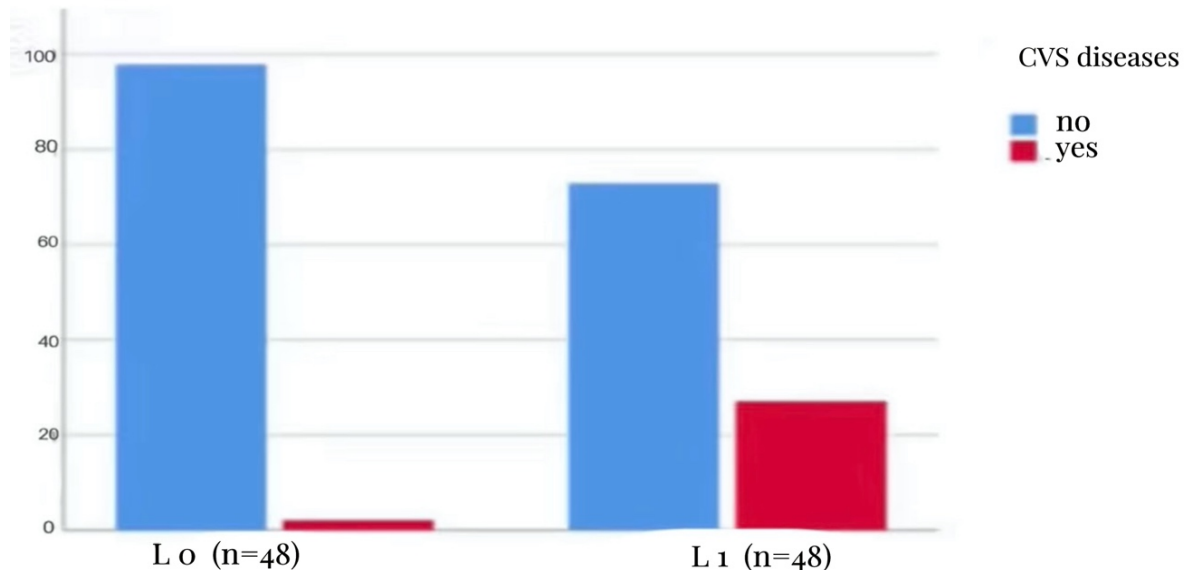
Note: * p = 0.001

Figure 2. **Distribution according to the frequency of cardiovascular system diseases (%)**

Arterial hypertension up to the time of admission was not determined in the group of pregnant women without PE, instead, it was determined in 33.3% (95% CI

21.3, 47.3) in pregnant women with PE. Thus, 33.3% of pregnant women with PE were receiving outpatient treatment or inpatient treatment with gestational hypertension, on the basis of which they developed PE, respectively we can establish that gestational hypertension is a risk factor for the development of PE (p < 0.001).

Mean values of systolic BP 168 mm/Hg and mean values of diastolic BP 103 mm/Hg (p<0.001).

IUGR during the current pregnancy was not present in the group of pregnant women without PE compared to the group of pregnant women diagnosed with PE, who had this complication in 16.7% of cases (95% CI 8.2, 29.0).

Examining the anamnestic data of the pregnant women from both groups we can select the patients who presented risk factors for PE, thus selecting the pregnant women who can later be subjected to laboratory and imaging screening for PE.

5. PARACLINICAL INFORMATION AND DOPPLER USG EXAMINATION INDICATIONS FOR PREGNANT WOMEN INCLUDED IN THE STUDY

5.1. Evaluation of the level of HIF-1a, IL-6, Doppler indices of the uterine artery and establishing their interrelationship in the prediction of preeclampsia

Ultrasound examination performed together with Doppler Velocimetry showed different results depending on the blood vessel studied. Thus, right uterine artery Doppler velocimetry PI ranged from a minimum of 0.59 to a maximum of 1.85, the mean was 0.98, and the values deviated from it by 0.29. Doppler velocimetry of the right uterine artery RI took values between 0.40 and 0.86, the mean was calculated 0.59, and the standard deviation 0.11. Doppler velocimetry of the right uterine artery S/D took values between minimum 1.70 and maximum 4.07, mean - 2.44 and standard deviation of 0.55.

Left uterine artery Doppler velocimetry PI ranged from 0.68 to 1.86, mean 1.11 and standard deviation 0.29. Doppler RI velocimetry of the left uterine artery took values between 0.44 and 0.94, mean 0.68 and standard deviation 0.11. S/D left uterine artery Doppler velocimetry ranged from 2.01 to 4.30, mean 2.72 and standard deviation 0.53.

The level of platelets in the group without PE between minimum 195 and maximum 320, the average being 267, and the standard deviation 33. In the group of pregnant women diagnosed with PE, platelets varied between 122 and 329, the average 208, and the standard deviation 47.

In the group of pregnant women with PE, the HIF-1A values were much higher compared to the first study group, thus, they varied between a minimum of 151.8 and a maximum of 985.1, the average was 601.1, and the standard deviation of 199.6.

The Mann-Whitney U test result of 1842.0 (p< 0.001), demonstrates a statistically significant difference in distribution between this criterion and the occurrence of PE.
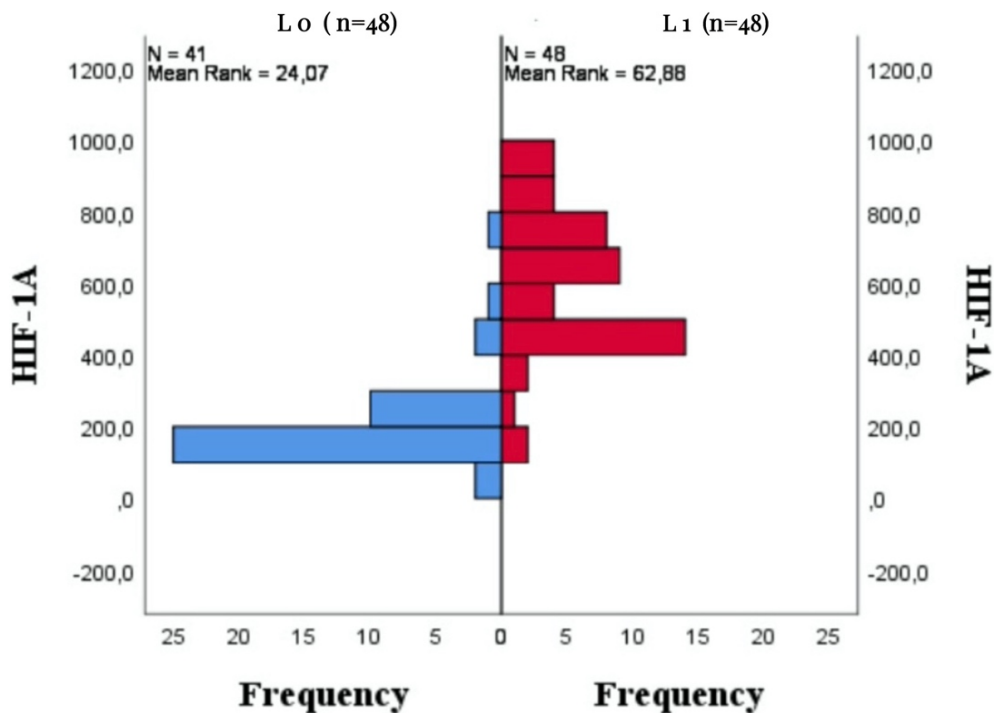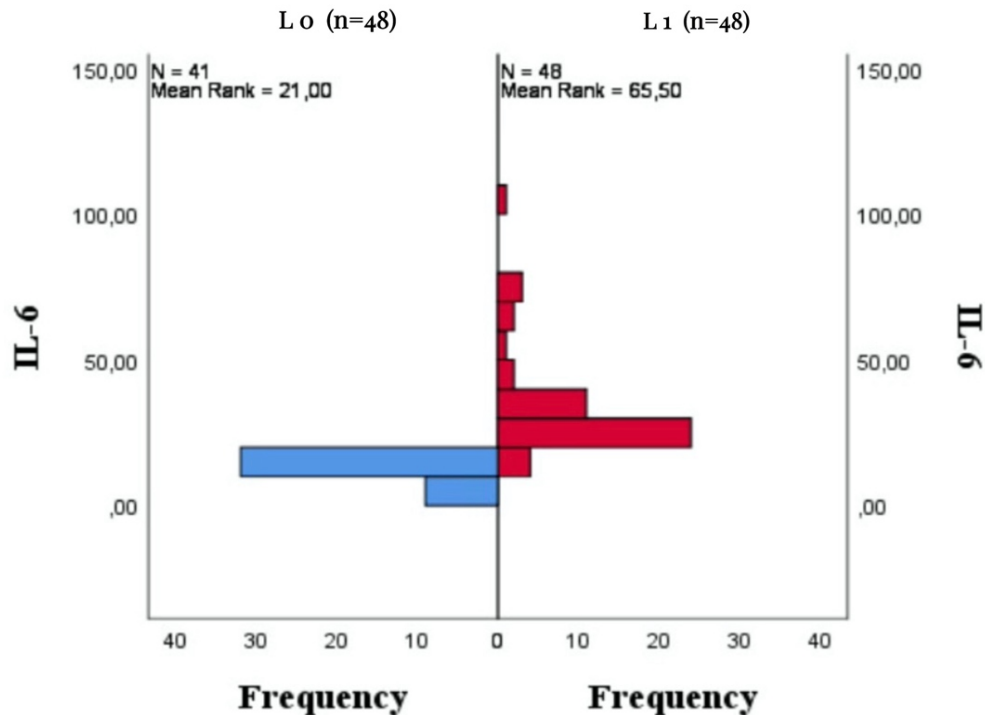
Note: * p < 0.001

Figure 3. **Comparative analysis of distribution by HIF-1A concentration measured in study groups (pg/ml)**

Another factor studied and described comparatively in the study groups, is IL-6, which varied in the group of pregnant women without PE, in an interval with a minimum of 4.12 and a maximum of 14.59. The average value was 10.59, and the standard deviation – 2.16.

In the group of pregnant women with PE, IL-6 values ranged between 15.57 and 104.71, the mean was 35.0, and the standard deviation was 18.41. The median value was 28.23, and the interquartile range varied between 24.30 and 37.61.

The distribution of values varied between groups, a fact demonstrated by the Mann-Whitney U test. Thus, $U = 1968.0$ ($p < 0.001$), a statistically significant result, was obtained, concluding that there is an association between IL-6 and PE.

Protein in the urine is one of the important criteria for the diagnosis of PE, thus, in the group of pregnant women without PE no protein was detected in the urine, on the other hand, in the group of pregnant women diagnosed with PE, the protein was detected in the urine and varied between 0.033 and 2.31, the mean took the value 0.77, and the standard deviation 0.46, ($p < 0.001$).

Note: * p < 0.001

Figure 4. **Comparative analysis of distribution by IL-6 concentration measured in study groups (pg/ml)**

The LDH varied between 220 and 390, in the group of pregnant women without PE, with an average of 294, and in the group of pregnant women with PE, the range of LDH values varied with a minimum of 64 and a maximum of 680, the average of was 490. The difference in the distribution of LDH values was demonstrated by the result of the Mann-Whitney test U = 216.0 (p < 0.001), statistically significant.

Analysis of correlations between HIF-1α, IL-6 and velocimetric indices

To identify possible correlations between HIF-1A, IL-6 and Doppler velocimetry indicators, the correlation matrix was created. As can be seen, the blood parameter HIF-1a had a correlation coefficient, statistically significant with IL-6 (CC=0.664, 95% CI 0.51, 0.73, p<0.001), with right uterine artery elvocimetry PI (CC=0.537 , CI95% 0.36, 0.66 p<0.001), with right uterine artery velocimetry RI (CC=0.502, CI95% 0.32, 0.63 p<0.001), with right uterine artery velocimetry S/D (CC=0.594, CI95% 0.46, 0.69 p<0.001), with velocimetry of the left uterine artery PI (CC=0.529, CI95% 0.36, 0.65 p<0.001), with velocimetry of the left uterine artery RI (CC=0.456, CI95% 0.26, 0.61, p<0.001) and with velocimetry left uterine artery S/D (CC=0.608, CI95% 0.46, 0.72 p<0.001).

Later, the blood parameter IL-6 also showed correlational relationships with some velocimetry results, with the velocimetry of the right uterine artery PI a moderate, statistically significant correlation is determined (CC=0.589, IC95% 0.41, 0.71, p<0.001), with the velocimetry of the right uterine artery RI (CC=0.628, CI95% 0.47,

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0.73, p<0.001) and with the velocimetry of the right uterine artery S/D (CC=0.692, CI95% 0.56, 0.77, p<0.001) the correlation was strong and statistically significant.

The correlation of IL-6 with PI left uterine artery velocimetry (CC=0.589, 95% CI 0.42, 0.71 p<0.001) and with RI left uterine artery velocimetry (CC=0.568, 95% CI 0.40, 0.70 p<0.001) was moderate, but statistically significant, on the other hand, the correlation with left uterine artery velocimetry S/D (CC=0.682, CI95% 0.57, 0.76 p<0.001) was strong and statistically significant.

The diagnostic test with the described predictors correctly determined the result for about 80% of the cases encountered. Sensitivity and specificity were 89.6% and 70.8% respectively, for the BMI variable, the Wald statistic demonstrates that the regression coefficient is significantly different from zero (Wald = 14.46, df=1, p <0.001).

The determined regression coefficient (B=0.383, p <0.001) demonstrates that increasing BMI is associated with increased chances of developing PE. Specifically, high BMI causes a 1.5 times greater chance of developing PE.
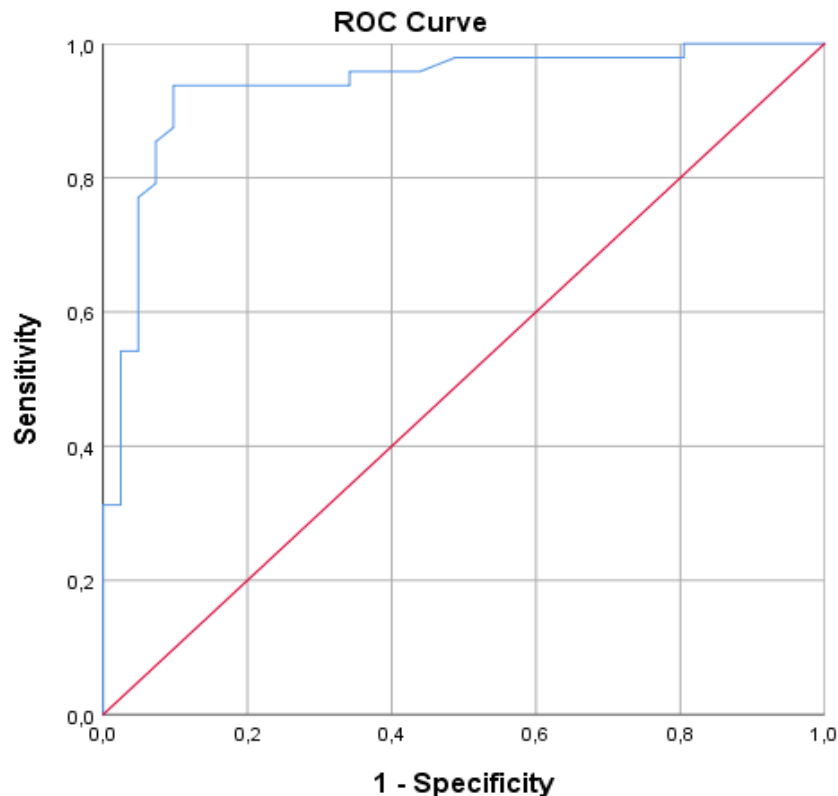
Figure 5. **ROC curve for the HIF-1a predictive model**

For the variable Cardiovascular diseases, the Wald statistic demonstrated that the regression coefficient is significantly different from zero (Wald = 5.464, df = 1, p < 0.001). Therefore, the determined regression coefficient (B= 2.565, p <0.001) denotes increased chances of developing preeclampsia by pregnant women who have cardiovascular diseases. More precisely, this variable determines about 13 times greater chances of developing PE.

For the variable HIF-1a, studied in the given model, the Wald statistic demonstrates that the regression coefficient is significantly different from zero (Wald = 26.913, df=1, p <0.001). The determined regression coefficient (B=0.013, p <0.001) demonstrates that HIF-1a is associated with increased chances to develop preeclampsia.

The optimal critical value of HIF-1a for predicting PE was estimated to be 320.65 with a Youden index of 0.84. This value indicates an optimal threshold that maximizes the difference between sensitivity and specificity, thus helping to improve the accuracy of PE prediction.

The area under the ROC Curve for the predictive model (HIF-1 a) was 0.936, which indicates a test with a very good diagnostic accuracy, with a 95% confidence interval (0.882, 0.990), and with a significant difference from the value of 0.5 (p<0.001).
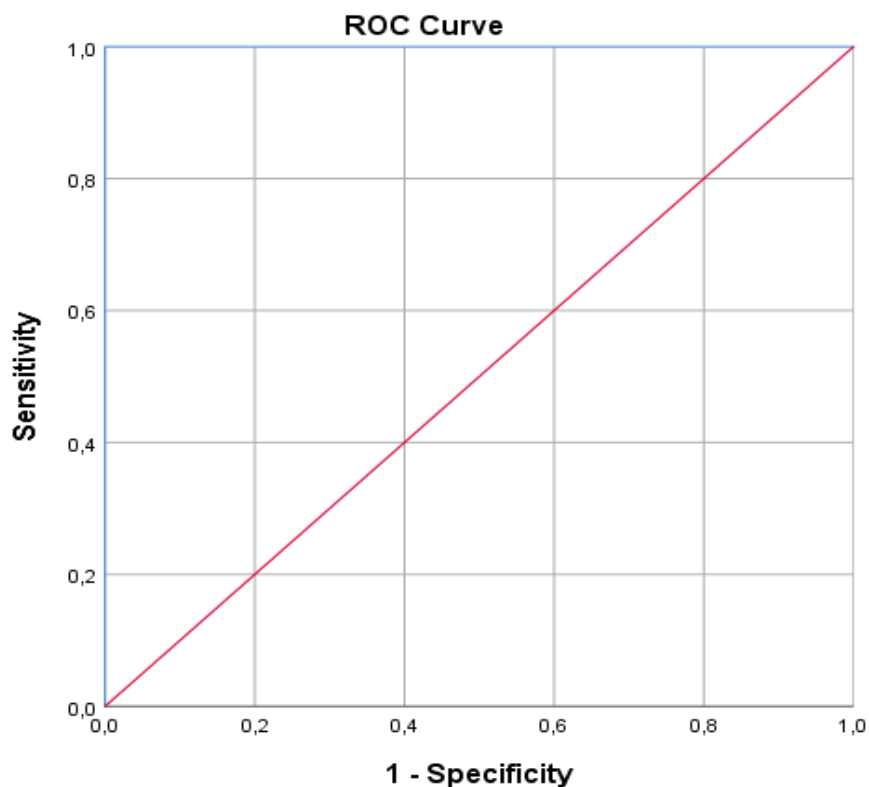
Figure 6. **ROC curve for the IL-6 predictive model**

The area under the ROC Curve for the predictive model (IL-6) was 1,000, indicating a test with excellent diagnostic accuracy, with a significant difference from the 0.5 value (p<0.001). It was calculated that the IL-6 diagnostic test makes a perfect difference between pregnant women with and without PE at a reference value equal to 15.08 pg/mL.

Characteristic of newborns

Fetal weight at birth was different between groups. Thus, in the first group, the weight varied between a minimum of 2900 and a maximum of 4000, the average was 3364. In the group of pregnant women diagnosed with PE, the weight of the fetus varied from 490 to 4440, the average was 2807. IUGR did not had no newborn in the

group of pregnant women without PE and 16.7% (95% CI 8.2, 29.0) had in the group of pregnant women with PE (p = 0.01). The post-natal evolution, in the group of pregnant women without a diagnosis of PE was completed with discharge in 100%, and in the case of pregnant women with a diagnosis of PE, it was completed with discharge in only 66.7%, and in the other cases 31.3% were transferred to stage II/III, with death in 2.1%.

The algorithm of conduct in the third trimester of pregnancy for pregnant women at risk of preeclampsia

In order to improve the criteria for predicting PE in the third trimester of pregnancy, an algorithm was developed (Figure 7). The key recommendations expressed in this algorithm are based on the results obtained in the research carried out. All the factors of the study were subjected to research using the logistic regression method. These factors were represented by the particularities of the obstetric anamnesis complicated by: early abortions in the anamnesis, premature births and re-eclampsia in the anamnesis, medical conditions existing during the pregnancy: cardiovascular disease, obesity. Later, the Doppler velocimetry (PI) parameters of the uterine arteries were evaluated in these patients.

Determination of maternal risk factors:
- Increased BMI, pathological weight gain, CVS conditions
- The presence of protein in the urine (insignificant values)
- Pregnant women with gestational hypertension or single episodes of hypertension

USG examination with Doppler of the uterine arteries (PI)
Assessment of HIF-1α and IL-6 concentration
Pregnancy period: from 29+0 w.a.

HIF-1a levels (<320,65 pg/ml)
IL-6 (<15.08 pg/ml)
Insignificant change in Doppler indices

Elevated levels of HIF-1a (>320,65 pg/ml)
IL-6 (>15.08 pg/ml)
Significant change in Doppler indices

Low risk of preeclampsia:
- Continuation of the pregnancy
- Monitoring in ambulatory conditions

Increased risk of preeclampsia:
- Assessment of the condition of the mother and the fetus, with more thorough surveillance
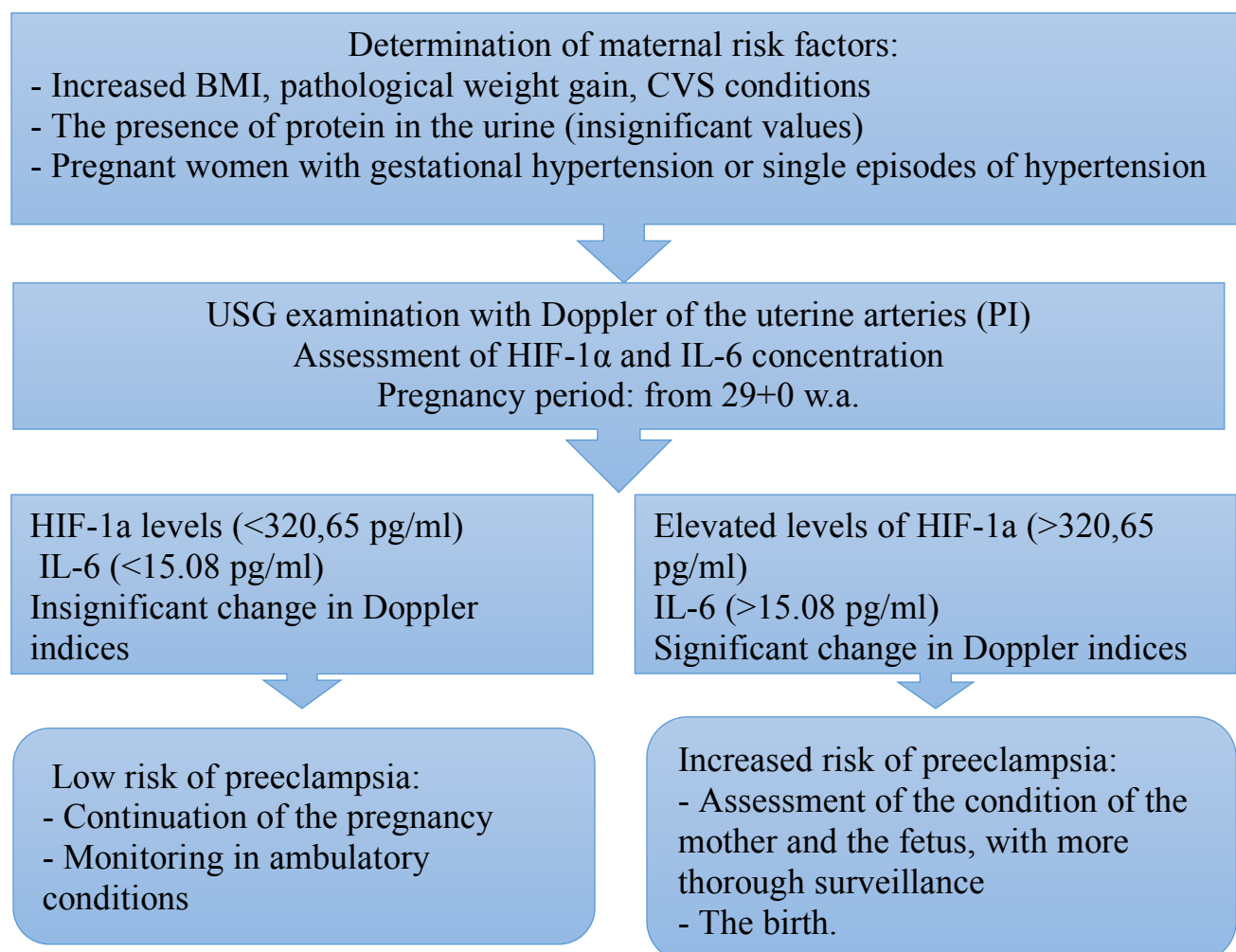- The birth.

Figure 7. **Behavior algorithm in the third trimester of pregnancy for pregnant women with risk of preeclampsia**

The next step was to examine the serum level of HIF-1a and IL-6 in maternal blood, which when reaching higher values of HIF-1a (>320.65 pg/ml), IL-6 (>15.08 pg/ mL), pregnant women are classified in the high risk group. In the case of classifying pregnant women in the group with high risk of PE, the clinical-paraclinical evaluation of the maternal condition (coagulogram, LDH, ALT, ASAT, platelet level, protein in urine in 24h, BP monitoring) and fetal (fetometry, CTG, Doppler AO) is recommended, with close supervision or completion of the pregnancy, depending on the maternal-fetal condition.

Following the application of the logistic regression method, these factors with a role in predicting PE were evaluated. In order to confirm the value of the given model, these factors were subjected to the ROC curve analysis. Thus, the ROC curve for the predictive model (HIF-1 a) was 0.936, which indicates a test with an acceptable diagnostic accuracy, with a 95% confidence interval (0.882, 0.990) (p<0.001), with a specificity of 90.2 % and the sensitivity of 93.8%, the model being able to determine 92 % of the cases. The optimal critical value of HIF-1a for predicting PE was estimated to be 320.65 with a Youden index of 0.84. This value indicates an optimal threshold that maximizes the difference between sensitivity and specificity, thus helping to improve the accuracy of PE prediction.

The ROC curve for the predictive model (IL-6) was 1,000, which indicates a test with very good diagnostic accuracy, the created model was able to determine the diagnosis in 100% of cases, with a specificity and sensitivity of 100%, the test diagnostic IL-6 can differentiate between pregnant women with and without PE at a reference value equal to 15.08 pg/mL.

Thus, summarizing the obtained data, we can conclude that a strong correlation coefficient was determined between the laboratory indices HIF-1a, IL-6, and Doppler velocity indices of the uterine arteries (PI), demonstrating the effectiveness of the overall examination complex of the Doppler indices of the arteries uterine (PI) and paraclinical indices HIF-1a and IL-6 for better accuracy, and could function as a test in predicting PE in the third trimester of pregnancy.

GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS
CONCLUSIONS

1. The most frequent manifestations associated with PE, present at the admission of pregnant women, were headache 93.8% (p < 0.001), epigastric pain 37.5% (p < 0.001), nausea/vomiting 12.5% (p = 0.035), visual disturbances 20.8% (p = 0.003), the presence of edema 93.8% (p <0.001) and mean values of systolic BP 168 mm/Hg and mean values of diastolic BP 103 mm/Hg (p<0.001). The occurrence of PE in the third trimester of pregnancy increases the risk of ending the pregnancy by caesarean section, which was established in the conducted study, where in the group of patients with PE it was performed in 93.8% of cases (p< 0.001).

2. Following the study, the major risk factors for the development of PE were identified, which include: high BMI (p < 0.001), diseases of the cardiovascular system, which included heart diseases, represented by various acquired or congenital heart

disorders (p = 0.001), pathological weight gain (p = 0.013), spontaneous abortions in the anamnesis (p<0.001) and stalled pregnancies in the anamnesis (p=0.012).

3. The results of the research show that the serum concentration of HIF-1a was significantly higher in the group of pregnant women with PE (p < 0.001), the threshold level of the HIF-1a index was estimated at 320.65 pg/ml, the given model being able to determine 92% of PE cases, with specificity of 90.2% and sensitivity of 93.8%. The level of IL-6 was also significantly higher in the group of pregnant women with PE (p < 0.001), the diagnostic test can make a very good difference between pregnant women with and without PE from a reference value equal to 15.08 pg/mL, with 100% specificity and sensitivity.

4. The scientific problem solved in the study was the optimization of the behavioral management of pregnant women at risk of PE, by developing the behavioral algorithm, which includes: the identification of maternal risk factors, the elevated serum level of HIF-1a (>320.65 pg/ml) and IL-6 (>15.08 pg/ml), pathological Doppler velocimetry (PI) indices.

PRACTICAL RECOMMENDATIONS

1. Pregnant women who present risk factors such as high BMI, pathological weight gain, CVS diseases, the presence of protein in the urine (insignificant values), pregnant women with gestational hypertension or with single episodes of arterial hypertension, will be included in the group of risk for PE development.

2. In patients whose risk factors for PE have been identified, it is recommended to evaluate the Doppler parameters of the uterine arteries (PI), investigate the serum level of HIF-1a and IL-6, to assess the risk of developing PE. In the case of classifying pregnant women in the group with high risk of PE, the clinical-paraclinical evaluation of the maternal condition (coagulogram, LDH, ALT, ASAT, platelet level, protein in urine in 24h, BP monitoring) and fetal (fetometry, CTG, Doppler AO), with close supervision or completion of the pregnancy, depending on the maternal-fetal condition.

3. In order to determine pregnant women with a high risk of PE in the third trimester of pregnancy, it is proposed to implement the behavioral algorithm developed in the study, which includes: identification of maternal risk factors, high serum level of HIF-1a (>320.65 pg/ml) and IL-6 (>15.08 pg/ml), pathological Doppler velocimetry index (PI).

4. Supplementing the educational-didactic program with information aimed at the behavior of patients at risk of PE, which can provide an effective and simple test to apply for the prediction of PE in the third trimester of pregnancy.

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ADNOTARE
Oleinic Vera
„Preeclampsia şi rolul factorilor de predicţie în trimestrul trei de sarcină''
Teză de doctor în ştiinţe medicale. Chişinău, 2024

Structura tezei. Lucrarea este expusă pe 103 de pagini, cu următoarea structură: cuprins, adnotare, lista abrevierilor, introducere, analiza bibliografică la tema tezei din literatura de specialitate, materiale şi metode de cercetare, rezultate proprii expuse în 3 capitole, sinteza rezultatelor obţinute, concluzii generale, recomandări practice, bibliografie ce include 120 de surse naţionale şi internaţionale, 44 de figuri, 6 tabele, 90 de anexe. Rezultatele obţinute sunt publicate în 9 lucrări ştiinţifice.

Cuvinte cheie: preeclampsie, markeri de predicţie, al treilea trimestru, ecografie Doppler.

Scopul studiului. Evaluarea rolului factorilor de predicţie a preeclampsiei în trimestrul trei de sarcină, pentru optimizarea managementului şi îmbunătăţirea prognosticului materno-fetal.

Obiectivele studiului. Stabilirea particularităţilor anamnestice şi evolutive ale sarcinii la gravidele cu preeclampsie în trimestrul trei de sarcină. Evaluarea factorilor de risc ce contribuie la apariţia preeclampsiei în tri   mestrul trei de sarcină. Aprecierea nivelului indicilor HIF-1a, IL-6, indicilor Doppler a arterelor uterine, şi stabilirea interrelaţiei acestora în prezicerea preeclampsiei. Stabilirea algoritmului de conduită pentru gravidele cu risc de a dezvolta preeclampsie.

Noutatea ştiinţifică a rezultatelor obţinute. Prin analizarea detaliată a factorilor de risc personali şi medicali asociaţi preeclampsiei, precum şi a evoluţiei sarcinii, cercetarea a contribuit la înţelegerea complexităţii acestei afecţiuni. Această abordare ne-a permis identificarea factorilor de risc, şi a demonstrat rolul biomarkerilor HIF-1a, IL-6 şi interrelaţia acestora cu indicii Doppler a arterelor uterine în prezicerea preeclampsiei. Realizarea algoritmului de conduită pentru prezicerea PE reprezintă o contribuţie în practica medicală, pentru a preveni apariţia complicaţiilor severe materno-fetale.

Problema ştiinţifică rezolvată în teză constă în determinarea rolului biomarkerilor HIF-1a, IL-6 şi indicilor Doppler a arterelor uterine în dezvoltarea preeclampsiei, iar rezultatele acestei cercetări confirmă relevanţa studiului.

Semnificaţia teoretică a lucrării. Rezultatele studiului extind baza teoretică pentru utilizarea biomarkerilor în prezicerea preeclampsiei. Au fost stabilite nivelurile prag pentru HIF-1a (>320,65 pg/ml) şi IL-6 (>15,08 pg/ml) care împreună cu parametrii Doppler (PI) a arterelor uterine modificaţi, sunt asociate cu un risc crescut de apariţie a preeclampsie. În baza rezultatelor primite a fost realizat algoritmul de conduită pentru prezicerea preeclampsiei în al treilea trimestru de sarcină.

Valoarea aplicativă a lucrării. Aplicarea algoritmului propus, ce constă în identificarea factorilor de risc materni, nivelul seric crescut a HIF-1a (>320,65 pg/ml) şi IL-6 (>15,08 pg/ml), indicele velocimetriei Doppler (PI) a arterelor uterine patologic, ne permit identificarea gravidelor cu risc de a dezvolta preeclampsie. Astfel, performanţa acestor biomarkeri este necesară pentru predicţia PE în trimestrul trei de sarcină. Rezultatele obţinute ne oferă informaţii teoretice extinse care pot fi folosite în practică pentru optimizarea managementului gravidelor cu preeclampsie.

Implementarea rezultatelor științifice. Rezultatele cercetării au fost implementate în activitatea curativă curentă a IMSP Spitalul Clinic Municipal *Gheorghe Paladi.*

АННОТАЦИЯ
Олейник Вера
Преэклампсия и роль прогностических факторов в третьем триместре беременности

Диссертация кандидата медицинских наук. Кишинэу, 2024 г.

Структура диссертации. Работа представлена на 103 страницах, включает оглавление, аннотации**,** список сокращений, введение, анализ литературы по теме диссертации, материалы и методы исследования, собственные результаты, представленные в 3 главах, обобщение полученных результатов, общие выводы, библиографию, включающую 120 отечественных и зарубежных источников, 44 рисунков, 6 таблиц, 90 приложений. Полученные результаты опубликованы в 9 научных работах.

Ключевые слова: преэклампсия, прогностические маркеры, третий триместр, допплерография.

Цель исследования. Оценка роли предикторов преэклампсии в третьем триместре беременности, для оптимизации тактики ведения и улучшения прогноза для матери и плода.

Задачи исследования. Установление особенностей анамнеза и течения периода гестации у пациенток с преэклампсией в третьем триместре беременности. Оценка факторов риска, способствующих возникновению преэклампсии в третьем триместре беременности. Оценка уровня HIF-1a, IL-6, показателей допплерографии маточных артерий и их сочетанных изменений в прогнозировании гипертензивных нарушений. Разработка алгоритма ведения беременных с риском развития преэклампсии.

Научная новизна полученных результатов. Подробно анализируя личностные и медицинские факторы риска, связанные с преэклампсией, а также течение беременности, исследование способствовало пониманию многогранности патогенеза этого состояния. Такой подход позволил выявить индивидуальные факторы риска и продемонстрировать роль биомаркеров HIF-1a, IL-6 в сочетании с показателями допплерографии маточных артерий в прогнозировании преэклампсии. Реализация алгоритма обследования с целью прогнозирования ПЭ представляет собой вклад в медицинскую практику, предотвращающую возникновение серьезных осложнений у матери и плода.

Научная задача, решённая в диссертации, заключается в обосновании сочетанного определения биомаркеров HIF-1a, IL-6 и допплерометрии кровотока в маточных артерии с целью прогнозирования преэклампсии, а результаты данного исследования подтверждают его актуальность.

Теоретическая значимость работы. Результаты исследования расширяют теоретические основы использования биомаркеров с целью прогнозирования

преэклампсии. Установлены пороговые уровни для HIF-1a (>320,65 пг/мл), IL-6 (>15,08 пг/мл) а также измененные параметры допплерографии маточных артерий (PI) связаны с повышенным риском преэклампсии. Эффективное их внедрение в медицинскую практику возможно на основании разработанного алгоритма прогнозирования преэклампсии в третьем триместре беременности.

Прикладная ценность работы. Применение предложенного алгоритма заключается в выявлении материнских факторов риска, повышении сывороточного уровня HIF-1a (>320,65 пг/мл) и IL-6 (>15,08 пг/мл), патологического индекса доплеровской велосиметрии маточных артерий (PI), позволяют выявить беременных женщин с риском развития преэклампсии. Таким образом, показатели этих биомаркеров необходимы для прогнозирования ПЭ в третьем триместре беременности.

Внедрение результатов. Результаты исследования внедрены в текущую лечебную деятельность Муниципальной клинической больницы ПМСУ имени Георгия Палади.

ANNOTATION
Oleinic Vera
„Preeclampsia and the role of prognostic factors in it third trimester of pregnancy''
PhD thesis in Medical Sciences. Chisinau, 2024

The structure of the dissertation. The work is presented on 103 pages, has the following structure: table of contents, annotation**,** list of abbreviations, introduction, bibliographic analysis on the topic of the dissertation from the specialized literature, research materials and methods, own results presented in 3 chapters, summary of the work. results obtained, general conclusions, bibliography, including 120 national and international sources, 44 figures, 6 tables, 90 applications. The obtained results were published in 9 scientific papers.

Key words: preeclampsia, prognostic markers, third trimester, Doppler ultrasound.

The purpose of the study. Assessing the role of predictors of preeclampsia in the third trimester of pregnancy to optimize management and improve maternal and fetal prognosis.

Objectives of the study. Establishing the anamnestic and evolutionary characteristics of pregnancy in pregnant women with preeclampsia in the third trimester of pregnancy. Evaluation of risk factors that contribute to the occurrence of preeclampsia in the third trimester of pregnancy. Assessment of the level of HIF-1a, IL-6, Doppler indices of uterine arteries, and establishment of their interrelation in predicting preeclampsia. Development of an algorithm for the management of pregnant women at risk of developing preeclampsia.

Scientific novelty of the results obtained. By analyzing in detail the personal and medical risk factors associated with preeclampsia, as well as the evolution of pregnancy, the research contributed to understanding the complexity of this condition.

This approach allowed us to identify risk factors, and demonstrated the role of biomarkers HIF-1a, IL-6 and their interrelation with Doppler indices of uterine arteries in predicting preeclampsia. The implementation of the behavioral algorithm for predicting PE represents a contribution to medical practice, in order to prevent the occurrence of severe maternal-fetal complications.

The scientific problem solved in the thesis consists in determining the role of biomarkers HIF-1a, IL-6 and Doppler indices of uterine arteries in the development of preeclampsia, and the results of this research confirm the relevance of the study.

Theoretical significance of the work. The results of the study expand the theoretical basis for the use of biomarkers in predicting preeclampsia. Threshold levels for HIF-1a ($>320,65$ pg/ml) and IL-6 (>15.08 pg/ml) were established, which together with altered uterine artery Doppler parameters (PI) are associated with an increased risk of preeclampsia. Based on the results received, a behavioral algorithm for predicting preeclampsia in the third trimester of pregnancy was developed.

Applicative value of the work. The application of the proposed algorithm, which consists of identifying maternal risk factors, elevated serum levels of HIF-1a (>320.65 pg/ml) and IL-6 (>15.08 pg/ml), pathological Doppler velocimetry index (PI), allows us to identify pregnant women at risk of developing preeclampsia. Thus, the performance of these biomarkers is necessary for the prediction of PE in the third trimester of pregnancy. The results obtained provide us with extensive theoretical information that can be used in practice to optimize the management of pregnant women with preeclampsia.

Implementation of scientific results. The research results were implemented in the current curative activity of IMSP SCM Gheorghe Paladi.