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Evaluation of Oxidative Stress in the Development of Postpartum Endometritis and Their Prognostic Significance

Umarov Aziz Rustamovich, Kamilova Iroda Abdurasulovna

Tashkent Medical Academy

Abstract: *The development of postpartum endometritis is characterized by aggravated obstetric-gynecological, somatic, social anamnesis and postpartum anamnesis with a high level of proinflammatory markers. The quality assessment of the predictive ability of the models was performed by using the Nagelkerke determination coefficient R^2, R^2 for an increase in the concentration of MDA is equal to = 85.67%; and for a decrease in AOA activity - 93.52%, which proves the higher prognostic significance of the obtained regression models.*

Key words: *endometritis, postpartum period, lipid peroxidation, antioxidant system, systemic inflammation, postpartum sepsis, malonic acid dialdehyde*

Introduction. The frequency of cesarean sections in Uzbekistan has been steadily increasing from 9.58% in 1999 to 16.10% in 2019. In perinatal centers of Uzbekistan in 2017-2020, an increase in the frequency of indications for CS was noted: the frequency of CS surgeries in perinatal centers in 2017 was 29.5%, in 2018 - 33.2%, in 2019 - 34.5% and in 2020 - 34.3%.

Postpartum endometritis (PE) is the most common maternal infection in the postpartum period, occurring after 1–3% of vaginal deliveries and in 27% of cesarean sections (CS), which is of great concern [18,22,23]. Despite medical advances and a downward trend, it often leads to prolonged hospitalization and rehospitalization, especially in developed countries [13,15,22,23,28]. Moreover, among deaths associated with puerperal sepsis, PE is the most common cause of death in the first 3–7 days after delivery [25]. Caesarean section is associated with a 5- to 10-fold increase in the incidence of postpartum infections and endometritis compared with vaginal delivery [25]. Moreover, the incidence of postpartum endometritis is approximately ten times higher in cesarean sections performed after the onset of labor than in elective ones [26]. To reduce obstetric complications, the frequency of caesarean sections recommended by WHO should not exceed 15–30% of the total number of births.

Several factors increase the risk of intrauterine infection after delivery. These include young maternal age, obesity, diabetes, immunosuppressive disorders, corticosteroid therapy, decreased frequency of antenatal care, chorioamnionitis, history of repeat cesarean section, urgent cesarean section, stapled wound closure, and excessive blood loss [4,5,9,10].

Systemic inflammation is associated with changes in the number and function of blood cell components. Hematological markers are considered to be a reflection of the systemic

inflammatory environment. The neutrophil-to-lymphocyte ratio is widely used to assess the severity of inflammation in postpartum infectious pathology. The role of neutrophils and lymphocytes in maintaining or spreading inflammatory cascades in the most common pregnancy complications and the effectiveness of assessing the neutrophil-to-lymphocyte ratio for diagnosing and predicting pregnancy-related complications as potential predictors of acute and chronic inflammatory gynecological and reproductive disorders have been proven [11,12,14]. Factors causing an inflammatory response are expressed by activation of circulating leukocytes, increased production of neutrophil activators and complement activity. In assessing the risk of developing infection after CS, a high prognostic potential was demonstrated by a complete blood count and various complete blood count variables, including hemoglobin, hematocrit, blood cells, their morphology , red blood cell volume, red blood cell distribution width, and systemic inflammation markers based on the ratios of various forms of leukocytes [16,19].

However, the information content of clinical blood analysis is low and changes characteristic of the inflammatory process are detected in no more than 60% of women in labor with endometritis [8], while the content of leukocytes and neutrophils, as predictors of postpartum endometritis in women in labor, does not have clinical and prognostic value and can only serve as a screening test to exclude purulent-inflammatory diseases in women in labor [6]

In this regard, the search for predictors of the development of postpartum endometritis is relevant and **the goal of our study:** to study the prognostic significance of lipid peroxidation and the activity of the antioxidant system of the blood in the early postpartum period in the development of postpartum endometritis.

Materials and methods: The study included 66 women in labor with postpartum endometritis of varying severity: 23 with mild course; 22 with moderate course and 21 with severe course; the control (comparison) group consisted of 23 women in labor with a physiological course of the postpartum period.

In all parturient women, the levels of LPO and the activity of AOS enzymes were assessed on the 3rd day after delivery. Statistical analysis was performed using the SPSS program (IBM, version 21). The results are presented as the mean (M), dispersion (õ) and standard deviation (± m); median (25% lower quartile - 75% upper quartile). The assumption of normal distribution was verified by the Shapiro- Wilk test (α=0.05). Comparison of intergroup differences for independent samples was performed using Tukey's pairwise comparison HSD / Tukey Kramer ANOVA program, for comparing quantitative data having a distribution different from normal, the Kruskal method was used Wallis , Spearman's method was used to identify correlations . Results were considered statistically significant at an error level of $p < 0.05$. ROC analysis was used to calculate the threshold level of values, concentrations of LPO products and activity of AOS enzymes, specificity and sensitivity of the methods.

The criteria for diagnosing postpartum endometritis were the results of clinical and laboratory examination of women in labor (Table 1).

Table 1.

Clinical characteristics of postpartum endometritis of varying severity in comparison groups

Indicator	Severity of postpartum endometritis			Control group m = 23
	Light m =23	Moderate m = 22	Severe m = 21	
T ° body °C	37.6±1.35[1]	38.4±1.62[12]	38.8±1.13[123]	36.5±1.23
Pain on palpation	0.77±0.03[1]	1.25±0.04[12]	2.45±0.12[123]	0.3±0.01

Discharges	0.69±0.02[1]	1.37±0.06[12]	2.65±0.12[123]	0.20±0.01
Intoxication symptoms	0.34±0.01[1]	1.15±0.05[12]	2.33±0.10[123]	0.35±0.02
Involution of the uterus	0.47±0.02[1]	0.85±0.03[12]	1.77±0.08[123]	0.25±0.01
Hemostasisogram	0.55±0.02[1]	1.08±0.04[12]	2.41±0.4[123]	0.25±0.01
Blood biochemistry	0.40±0.01[1]	1.25±0.06[12]	1.92±0.09[123]	0.21±0.01
Blood formula	0.65±0.03[1]	1.90±0.08[12]	2.35±0.10[123]	0.37±0.02

Note: [1]- $p<0.05$ in relation to the control group; [2]- $p<0.05$ in relation to the mild course group; [3]- $p<0.05$ in relation to the moderate and severe course group.

Despite the large number of primary etiological factors, the immediate cause is microbial invasion with subsequent inflammatory damage to the endometrium [1,2], an indispensable attribute of inflammation is oxidative stress [2,3], which determines the importance of studying the processes free radical oxidation. The content of the final product of lipid peroxidation of cell membranes is malonic Dialdehyde (MDA) in the blood plasma of women in labor with endometritis statistically significantly exceeded the corresponding control values and progressively increased in women in labor with a more severe course.

Post hoc comparisons of mean group MDA levels using Tukey's method showed that statistically significant differences in the analysis of variance were associated with differences in mean MDA values in all three groups.

The difference in the results of the study of MDA concentrations in the comparison groups is clearly seen in Fig. 1. Moreover, with an increase in the severity of postpartum endometritis, the concentration of MDA in the blood significantly increased. As can be seen from Fig. 1, the concentration of MDA in moderate PE exceeded the level of mild PE by 1.12 μmol / l ($p \leq 0.001$); in severe PE, this difference was 4.70 μmol / l ($p \leq 0.001$); and the difference between mild PE and the control was 0.55 μmol / l ($p \leq 0.001$); between moderate PE and the control 1.67 μmol / l ($p \leq 0.001$); and between severe PE and the control 5.24 μmol / l ($p \leq 0.001$).

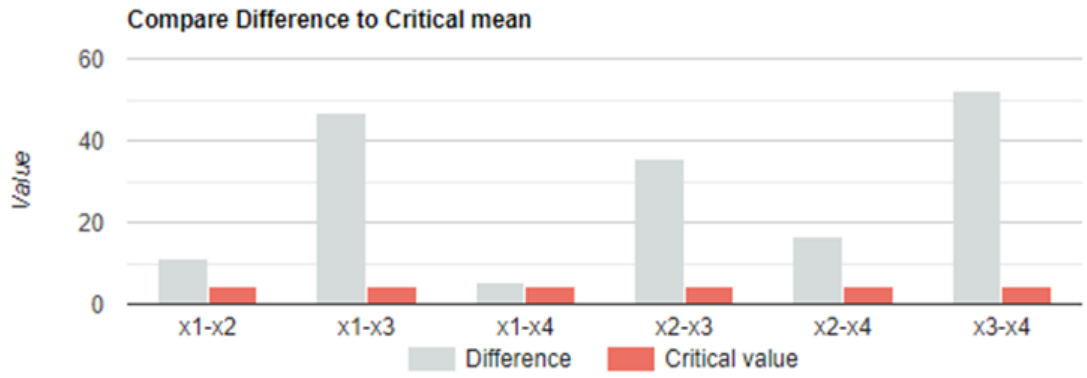

Fig. 1. Difference between the critical mean and meangroup values of MDA in comparison groups

Oxidative stress is a condition in which the antioxidant system fails to cope with the overproduction of reactive oxygen species, leading to oxidation of the main cellular macromolecules and proteins of cell membranes and molecular dysfunction. MDA is the end product of peroxidation of polyunsaturated fatty acids of cell membranes and is recognized as a marker of oxidative stress and antioxidant status [20,24]. Thus, the progression of PE contributes to an increase in the production of reactive oxygen species (ROS) and an increase in the severity

of endometritis itself. Evaluation of antioxidant activity (AOA) demonstrated the opposite direction - with an increase in the severity of PE, the total AOA activity significantly decreased.

Post-hoc comparisons of mean group indicators of AOA activity using the Tukey - Kramer method in the ANOVA analysis showed that statistically significant differences in the analysis of variance are associated with differences in the mean values of AOA in the comparison groups.

The difference between the critical average and average group AOA activity (in%) in the comparison groups demonstrates a decrease in AOA with increasing severity of PE (Fig. 2).

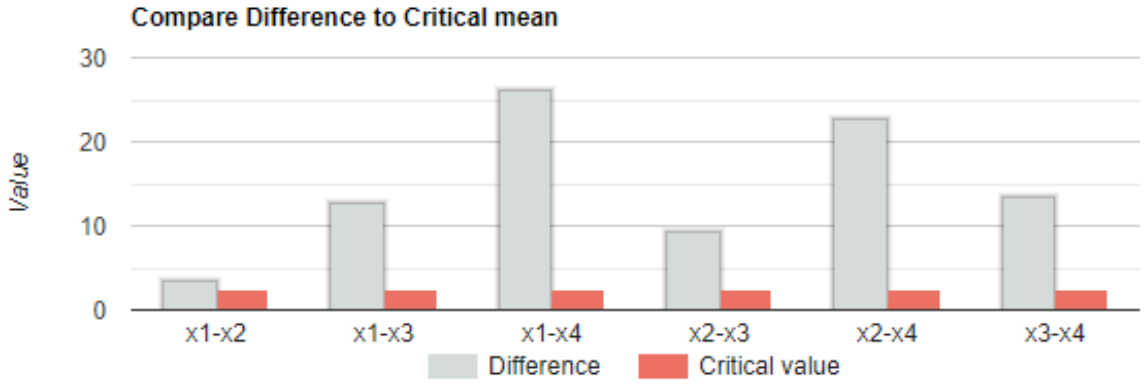

Fig. 2. Difference between critical average and average group AOA activity (in %) in comparison groups

In Fig. 2, the critical average value of AOA in % in group 4 – severe course of PE – is taken as the critical average, while the difference between the critical average and average group activity of AOA in women in labor without PE and with severe course (X1 – X4) is -26.13 AOA units; with moderate and severe course (X2 – X4) – 22.74 AOA units; the corresponding difference between moderate and severe course is 13.46 AOA units, etc. (Fig. 2).

The priority of studying oxidative stress in PE is determined by the need to understand the pathophysiological mechanisms underlying conditions associated with the development of endometrial inflammation in the postpartum period. Oxidative stress is defined as an imbalance between reactive oxygen species (ROS) and antioxidants, which may be involved in the pathophysiology of endometritis and the general inflammatory response of the body.

Total antioxidant capacity (activity) (AOA) is a biological parameter representing the sum of antioxidant effects of enzymatic antioxidants and molecules with antioxidant properties in a living organism, reflecting the ability to negate the negative impact of free radicals at the cellular level [26,27]. Determination of total antioxidant activity as the integration activity of several antioxidants in plasma is important in the analysis of biological systems. A decrease in AOA with increasing severity of PE reflects the role of pathogenetic mechanisms of oxidative stress in the severity of PE.

The diagnostic performance of a test is the accuracy of the test in distinguishing disease cases from normal controls. ROC curves can also be used to compare the diagnostic performance of two or more laboratory tests.

If the MDA concentration in the blood is more than 7.18 μmol/l, a conclusion can be made about a high risk of developing postpartum endometritis with a diagnostic sensitivity of 79.41% and a diagnostic specificity of 13.04%. If the AOA concentration is less than 40%, a conclusion can be made about a high risk of developing postpartum endometritis with a diagnostic sensitivity of 80.30% and a diagnostic specificity of 17.39%.

To compare the effectiveness ROC (Receiver Operator Characteristic) analysis was performed on the MDA level and AOA concentration, which is an analysis of characteristic curves

with the calculation of the area under the ROC curves AUC (Area Under Curve). Clinical informativeness of MDA level and AOA concentration using ROC analysis: the AUC (area under the curve) value for MDA was 88.27%, R^2 = 85.67%; for AOA, the AUC value was 82.40%, R^2 = 93.52%. The AUC value of 88.27% for MDA corresponds to a good model; the predictive value of AOA with an AUC of 82.40% is lower than that of MDA. The area of the AUC curve in the range of 0.9-1.0 is considered the highest informativeness of the diagnostic method, in the range of 0.8-0.9 - good informativeness, in the range of 0.7-0.8 - satisfactory, in the range of 0.6-0.7 - mediocre informativeness, and below - useless classification.

MDA - Y = 0.12 ln (x) + 1 AOA - Y = 0.18 ln (x) + 1

R^2 = 85.67% R^2=93.52%

Area under currea 88.27% Area under currea 82.40%

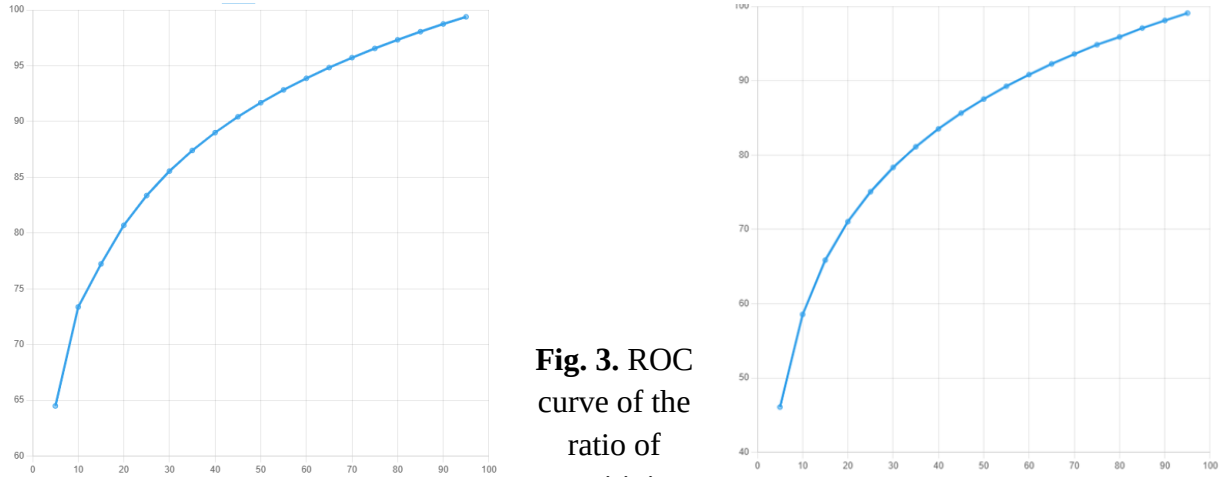

Fig. 3. ROC curve of the ratio of sensitivity and specificity of the prediction of the occurrence of postpartum endometritis based on the level of MDA and AOA activity (in%) in blood plasma.

Linear regression models for the risk of developing PE at different concentrations of MDA have the form: Y = 0.12ln(x) + 1; and for known values of AOA activity - Y = 0.18ln(x) + 1.

The quality of the predictability of the models was assessed using the Nagelkerke determination coefficient R^2, which is the main indicator of the quality of the regression models describing the relationships between the dependent and independent variables . The Nagelkerke determination coefficient R^2 reflects the specific weight of the contribution of changes in the studied inflammatory factors to the prognosis of the development of postpartum endometritis.

The R^2 value should be in the range from zero to one: $0 \leq R2 \leq 1$. The model is considered to be of higher quality if the value of the determination coefficient is close to 1. The statistical indicator shows what part of the variability of the observed variable can be explained by the constructed model, i.e. the value of the determination coefficient determines the share (in percent) of changes due to the influence of factor characteristics in the total variability of the resultant characteristic. R^2 for an increase in MDA concentration is 85.67%; and for a decrease in AOA activity - 93.52%, which proves the higher predictive significance of the obtained regression models.

Discussion. The presence of increased concentrations of free radicals and decreased antioxidant potential leads to oxidative stress. The development of oxidative stress may be one of the links in the chain of events leading to endometritis. Levels of oxidation -reduction potential can modulate the severity and dynamics of endometritis, and disease progression, biomarkers are associated with the level of oxidative stress with the severity of endometritis.

In uncomplicated pregnancy, there is a balance between the antioxidant system and reactive intermediates, but this balance can be disrupted by pregnancy complications or delivery with an unfavorable outcome [29]. The imbalance between prooxidant and antioxidant factors leads to oxidative stress, which contributes to the development of many diseases. This oxidative aggression can be a precursor to pathologies in the pregnant woman [15].

It is recognized that oxidative stress plays a central role in the pathophysiology of many disorders of pregnancy and the postpartum period, including pregnancy complications such as placental pathology, preeclampsia (PE), intrauterine growth restriction (IUGR), gestational diabetes and miscarriage [11,12] in the pathophysiology of oxidative stress in obstetric complications, the role of harmful habits, including alcohol abuse, is high [11,12,21].

Our results show that there was a significant increase in lipid peroxidation and a significant decrease in antioxidant status in parturient women with postpartum endometritis compared to the control group. This imbalance leads to a significant increase in the oxidative stress index in parturient women with postpartum endometritis.

The etiologic role of oxidant-antioxidant system disturbance during pregnancy in relation to adverse pregnancy outcomes has been proved. Oxidative stress can lead to numerous pathological conditions during female reproductive processes, contributing to the development of endometriosis , polycystic ovary syndrome, and various forms of infertility. Excessive ROS production can lead to fetal developmental disorders and increases the risk of miscarriage, intrauterine growth retardation, preeclampsia , premature birth, and gestational diabetes [15,17].

Conclusion. The development of postpartum endometritis is characterized by aggravated obstetric-gynecological, somatic, social anamnesis and postpartum anamnesis with a high level of proinflammatory markers. The developed method for predicting the development of postpartum endometritis allows identifying women in labor with a high risk of endometritis in an obstetric hospital at the preclinical stage of the disease, preventing the occurrence of severe purulent-septic complications after childbirth and is one of the measures to reduce maternal mortality.

Biochemical studies with determination of MDA and AOA in blood serum are useful as diagnostic methods for determining the risk of postpartum endometritis , significantly narrowing the range of studies and allowing to assess the risk of endometritis with high diagnostic accuracy using a limited range of studies.

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