

Bichevska R. G., Loskutova I. V. Manifestation of oxidative stress during pregnancy in women with chronic diseases of hepatobiliary system against the background of reproductive losses. Journal of Education, Health and Sport. 2021;11(04): 177-184. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2021.11.04.018>
<https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.04.018>
<https://zenodo.org/record/5090814>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

© The Authors 2021;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike.
(<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 26.02.2021. Revised: 31.03.2021. Accepted: 30.04.2021.

MANIFESTATION OF OXIDATIVE STRESS DURING PREGNANCY IN WOMEN WITH CHRONIC DISEASES OF HEPATOBILIARY SYSTEM AGAINST THE BACKGROUND OF REPRODUCTIVE LOSSES

R. G. Bichevska¹, I. V. Loskutova²

¹Municipal non-profit enterprise "Maternity hospital № 7", Odessa City Council,
Ukraine;

²Luhansk State Medical University, Rubizhne, Ukraine

Loskutova 0000-0002-0673-537X
Bichevskaya 0000-0003-1603-5171

Abstract

In the early stages of gestation the changes in the lipid peroxidation can lead to violations of regulatory and protective functions of biomembranes in pregnant women. **The objective:** to study the changes in the concentration of intermediate and final products of LPO during the first trimester of gestation in patients with early miscarriage against the background of chronic diseases of the hepatobiliary system. **Materials and methods.** 118 pregnant women in the first trimester of gestation (7-10 weeks), aged 22 - 39 y. o. (mean age 29.4 ± 2.7 years) have been examined. 64 women (54.2%) were diagnosed with a risk of miscarriage, and 17 patients were diagnosed with involuntary miscarriage within 10-12 days. All women were diagnosed with non-viral and non-alcoholic chronic HBS pathology: hepatic steatosis had 38 patients (32.2%), 80 patients (67.8%) had non-alcoholic steatohepatitis; in 97 patients (82.2%) chronic non-calculous cholecystitis was diagnosed. The state of lipid peroxidation was assessed by the content of malonic dialdehyde

spectrophotometrically, as well as diene conjugates in the blood. The indicator of erythrocyte peroxide hemolysis was examined by the level of erythrocyte peroxide resistance. **Results.** A significant increase in intermediate and final products of lipid peroxidation in pregnant women with an unfavorable premorbid background in the form of chronic diseases of the hepatobiliary system and a history of reproductive losses. A significant increase of MDA and DC concentration was found at the risk of premature termination of pregnancy. The degree of PLO processes activation makes these parameters integrative criteria for the detection of systemic metabolic disorders during gestation in women with GBS extragenital pathology. **Conclusion.** During physiological pregnancy there is an accumulation of metabolites of lipid peroxidation, which is associated with an increase in basic metabolism in women and an increase in oxygen consumption from the blood.

Key words: extragenital pathology; pregnancy; chronic disease of hepatobiliary system; systemic metabolic disorder.

Introduction. In the early stages of gestation the degree of biochemical changes is considered the most important because in this period the parameters of the lipid peroxidation (LPO) system - antioxidant protection are the most labile, which can lead to violations of regulatory and protective functions of biomembranes in pregnant women [7; 10; 11]. During physiological pregnancy, the rate of initiated oxidation increases, while there is no significant difference between these indicators at the 3-6 and 8-12 weeks of pregnancy [13; 18]. However, the high concentration of hydroperoxides in plasma, increased oxidation and the rate of initiated LPO indicate the intensification of this process already in early pregnancy.

It is the activation of free radical oxidation reactions that is the trigger for complications (gestosis, miscarriage, fetoplacental insufficiency) during pregnancy [13; 14; 16; 19]. This is considered as oxidative stress, which occurs when the balance between prooxidants and components of the antioxidant defense system (ADS) is damaged. As a result of activation of peroxidation processes, a toxic metabolite of LPO, in particular malonic dialdehyde (MDA), is synthesized as a biomarker of cell membrane destruction with accumulation of ROIs and increase of oxidative stress in the cell. This forms a pathological range of reactions, which has an unfavorable course in the formation of the placental complex and is a significant factor in the development of obstetric complications [3; 6; 10; 12].

Thus, high risk of obstetric pathology pregnant women exhibit higher rates of peroxidation.

During pregnancy, hepatic functional reserves are mobilized to neutralize the products of fetal life and provide it with plastic material. Deviations of some indicators from the norm should be considered as manifestations of metabolic activity and adaptation of a pregnant woman, so when examining women with physiological pregnancy they can detect palms erythema and vascular asterisks, and reduced gallbladder motility leads to gallstones [5; 9; 20]. During pregnancy, physiological changes in the biliary system often occur due to a complex of metabolic and hormonal changes. However, in some women after pregnancy, these changes pass from physiological to pathological conditions [17; 22; 23; 24].

The objective: to study the changes in the concentration of intermediate and final products of LPO during the first trimester of gestation in patients with early miscarriage against the background of chronic diseases of the hepatobiliary system (HBS).

Materials and methods

118 pregnant women with a gestational period of 7-10 weeks (first trimester), admitted to the in-patients unit. The patients aged 22 - 39 y. o. (mean age 29.4 ± 2.7 years). Among those examined, 64 women (54.2%) were diagnosed with a risk of miscarriage at the time of admission to the hospital, and 17 patients from this group were diagnosed with involuntary miscarriage within 10-12 days. Threatening miscarriage was diagnosed by clinical symptoms and ultrasound examination results.

All women under observation were diagnosed with non-viral and non-alcoholic chronic HBS pathology: hepatic steatosis had 38 patients (32.2%) and 80 patients (67.8%) had non-alcoholic steatohepatitis (NASH); in 97 patients (82.2%) chronic non-calculous cholecystitis (CNCC) was diagnosed. At the moment of examination clinical and laboratory signs of moderate exacerbation of HBS pathology were detected in 29 (24.6%) patients, the rest 89 patients (75.4%) had clinical remission.

The control group consisted of 39 women with repeated physiological pregnancy (first trimester) aged 21 - 37 y. o. without clinical, laboratory and instrumental signs of HBS pathology. The control group women did not have a history of abortions and miscarriages, and previous pregnancies ended in physiological childbirth.

Along with routine methods of examination, special biochemical tests characterized LPO intensity were used. The state of lipid peroxidation was assessed spectrophotometrically by the content of malonic dialdehyde (MDA) [1] and diene conjugates (DC) in the blood [4]. The indicator of erythrocyte peroxide hemolysis (EPH) was examined by the level of erythrocyte peroxide resistance [2].

Statistical processing of the results obtained was performed with the use of one- and multivariant dispersive analysis of variance (Microsoft Office 2003, Microsoft Excel Stadia 6.1 / prof and Statistica software packages).

In the analysis of the results we used the verification of the normality of the distribution of a random variable, Student's criterion to determine possible error limits (in the form of $M \pm m$, where M is the average value of the indicator, m is the standard error of the average value), correlation analysis (r).

Results and discussion

The intensity of free radical processes in the blood of pregnant women was assessed by the content of the final product (MDA) and primary metabolites (DC) of lipid peroxidation (Table 1). The concentration of DC in the blood of physiologically pregnant women averaged out (6.6 ± 0.2) $\mu\text{mol} / \text{l}$ (in health (6.3 ± 0.15) $\mu\text{mol} / \text{l}$; $P = 0.30$). More than in half of patients (20 persons) the level of primary metabolites increased to (6.9 ± 0.12) $\mu\text{mol} / \text{l}$ ($P < 0.05$), and in the rest of the persons under examination its value did not differ from norm significantly.

At the same time, during physiological pregnancy, a gradual increase in the final product POL - MDA to (3.9 ± 0.2) $\mu\text{mol} / \text{l}$ (in health (3.6 ± 0.2) $\mu\text{mol} / \text{l}$; $P < 0.01$) took place. As a result of the examination of women during the first trimester of gestation. There was an increase in the resistance of erythrocytes according to EPH in the I trimester of pregnancy. Thus, its value was 1.3 times higher in pregnant women than in non-pregnant ones (in health (3.1 ± 0.25)%; $P = 0.24$) (Table 1).

Table 1

LPO indexes in physiologically pregnant women ($M \pm m$)

Indexes	norm	control group n=39	P
MDA, $\mu\text{mol} / \text{l}$	$3,6 \pm 0,1$	$3,9 \pm 0,2$	$< 0,01$
DC, $\mu\text{mol} / \text{l}$	$6,3 \pm 0,15$	$6,6 \pm 0,2$	$= 0,30$
EPH, %	$3,1 \pm 0,25$	$3,5 \pm 0,3$	$= 0,24$

Note: P – significance has been calculated between indicators of control group and norm

This can be explained by the fact that immediately after conception there was a significant restructuring of the vital functions of pregnant women, which is associated with changes in blood systems, hemostasis, endocrine, immune system and changes in the biochemical state of the body as a whole. As a result of such changes in tissues and organs there is a certain stress, resulting in a sharp increase in the number of free radicals, which, among other things, attack the cells of the embryo [3; 8; 15].

There were significant shifts in metabolism in the first trimester of gestation in subjects with chronic pathology of GBS and burdened reproductive history (Table 2). The level of MDA in the serum of patients in the groups under examination was higher than that in physiological pregnancy (control group) 1.36 times, and equaled to $(5.3 \pm 0.3) \mu\text{mol} / \text{l}$ ($P < 0,001$). The increase of MDA concentration the blood serum during pregnancy in women with a burdened premorbid background indicated the intensification of the processes of lipid peroxidation of vascular endothelial cell membranes. In the patients under examination, DC concentration increased at 1.27 times compared to the control group ($P < 0.001$), and equaled to $(8.3 \pm 0.18) \mu\text{mol} / \text{l}$. The high content of LPO primary metabolites (DC) during pregnancy in women with chronic diseases of GBS and HB in the early stages in the anamnesis testified to the severity of metabolic shifts, which were characterized by a predominance of catabolic reactions. The rate of EPH in the women under examination in the first trimester of gestation increased at 1.69 times (up to $(5.9 \pm 0.2)\%$, while in the control group it was $(3.5 \pm 0.3)\%$; $P < 0.001$) (Table .2). Askarbayev K. A. et al. (2016) established that the reduction of erythrocytes' resistance, changes in the structural and functional properties of membranes, affected the adaptive processes in the fetus.

Thus, during gestation in women with a history of reproductive losses at the background of GBS pathology, lipid peroxidation was much higher than in physiologically pregnant women. This indicated the activation of LPO processes with the formation of toxic radicals.

The maximum growth of lipid peroxidation products was found in women with risk of abortion (Table 2).

Table 2

Indicators of LPO in the first trimester of gestation in patients with a burdened premorbid background ($M \pm m$)

Indicator	Control group	Pregnant women with a burdened obstetrical history (n= 118)		P
		Group of observation (n=54)	Patient with the risk of abortion (n=64)	
MDA, $\mu\text{mol} / \text{l}$	$3,9 \pm 0,2$	$5,3 \pm 0,3^{***}$	$7,8 \pm 0,4^{***}$	$< 0,001$
DC, $\mu\text{mol} / \text{l}$	$6,6 \pm 0,2$	$8,3 \pm 0,18^{***}$	$9,7 \pm 0,24^{***}$	$< 0,001$
EPH, %	$3,5 \pm 0,3$	$5,9 \pm 0,2^{***}$	$8,4 \pm 0,4^{***}$	$< 0,001$

Note: significant difference at $P^{***} - < 0,001$ between group of examined and control group; P - significance between indicators of the group of observation and the group with the risk of abortion

The content of the final metabolite (MDA) of lipid peroxidation was twice higher than in the control group ($P < 0.001$) and almost one and a half times higher than in women in the group under observation ($P < 0.001$). The concentration of the primary product of LPO (DC) was 1.47 times ($P < 0.001$) and 1.17 times ($P < 0.001$) higher than in the control group. The value of EPH increased most significantly at the risk of miscarriage, i. e. it was 2.40 times higher than the same indicator in the control group ($P < 0.001$) and 1.42 times ($P < 0.001$) in the observation group. Such high LPO rates can be explained by the presence of chronic GBS diseases, and pregnancy, in turn, as a stress factor contributes to the activation of free radical oxidation processes with destabilization of cell biomembranes (EPH index).

Thus, the special significance of the violation of lipid peroxidation processes in the pathogenesis of pregnancy complications (early miscarriages) in women with a burdened premorbid background (the presence of GBS chronic pathology) has been demonstrated.

Conclusions:

1. During physiological pregnancy there is an accumulation of metabolites of lipid peroxidation, which is associated with an increase in basic metabolism in women and an increase in oxygen consumption from the blood.

2. A significant increase in intermediate and final products of lipid peroxidation in pregnant women with an unfavorable premorbid background in the form of chronic diseases of the hepatobiliary system and a history of reproductive losses was found.

A significant increase of MDA and DC concentration was found at the risk of premature termination of pregnancy. The degree of PLO processes activation (by of MDA and DC levels) makes these parameters integrative criteria for the detection of systemic metabolic disorders during gestation in women with GBS extragenital pathology.

References:

1. Andreyev L. I., Kozhemiakin L.A. Determination of malonic malonic dialdehyde // Laboratory practice. - 1988. - № 11. - C. 41 – 43.
2. Afonina G. B., Kuyun L. A. Lipids, free radicals and immune response.- Kiev: NMU, 2000. - 285 p.
3. Voropayeva Ye. Ye., Sinitskiy A. I. Free radical processes in patients with early miscarriage // Ural Medical J. - 2011. - № 1 (79). – P. 101 - 104.
4. Gavrilov V. B., Mishkorudnaya M. I. Spectrophotometric determination of lipids hydroxides in blood serum // Laboratory Practice. - 1983.- №3. - P. 33 - 36.

5. Goliiianovsky O. B., Zhuravliova L. A., Savonik A. O. Course of pregnancy, labors and after labor period in women with hepatobiliary system diseases // *Perinatology and phthisiology*.- 2016. - №3 (67). – P. 23 - 27.
6. Goncharova B. C. Genotoxic signs of oxidative stress in genesis of early miscarriage : Synopsis of candidate thesis in medicine (specialty 14.01.01.) .- Moscow, 2016. – 22 p.
7. Iskhakov I. R., Iskhakov R. S., Farkhutdinov R. R. Estimation of the free-radical state on the statges of early embryogenesis // *medical herald of Bashkortostan*. - 2014. - Vol. 9. - № 5. - P. 135 - 137.
8. Kazimirko N. K., Akimova N. K., Akimova Ye.Ye., Zavadskiy V. Yu., Poliakov A. S., Tatarenko D. P. Immunology of physiological pregnancy // *Young Scholar*.- 2014. - № 3 (06). -P.132-138.
9. Karpeye S. A., Grinevich B. B., Karpeyeva Yu. S., Balukova Ye.V. Estimation of hepatobiliary system state in patients with habitual early miscarriage // *Gastroenterology (San Petersburg)*. - 2017. - № 1. - P. 83-83a.
10. Kovaliev Ye. V., Spiridonov Ye. V. Lipids peroxidation and anti-odidant activity aof amniotic liquid as a key biochemical process at pregnancy // *Dysfunction of endothelium: experimental and clinical researches / Materials of X Jubilee International Conference*. - 2018. -P. 127-131.
11. Kolobova C. O. Importance of oxidative stress in the development of early miscarriage // *Remedium Privolzhie*. - 2013. - № 3. - 33 p.
12. Mozhayeva T. A. meaning of monocytic / macrophagal cells in pathogenesis of early miscarriage : Synopsis of a candidate thesis in medicine (Specialty : 14.01.01) .- Ivanovo, 2014. - 22 p.
13. Omarov N. S., Radzhabova Sh. Sh., Cherkesova A. U., Cherkesova D. Y. Indexes of oxidative-anti-oxidant system at the threat and different clinical variants of premature early labors // *Russian Herald of Obstetrician-Gynecologist*. - 2018. - Vol. 18. - № 4. - P. 11-15.
14. Sidorova I. S., Unanian A. L. Early miscarriage: damage of anti-oxidative defence and its correction // *Russian Herald of Obstetrician-Gynecologist*.- 2009. - Vol. 9. - № 1.- P. 14-16.
15. Skripnichenko Yu. P., Baranov I. I., Vysokykh M. Yu., Arslanian K. N., Nesterova L. A. Oxidative-reduced reaction in pregnant - a key to prediction of gestation complications // *Obstetrics and Gynecology. News. Opinions. Training*.- 2017. - № 2 (16). – P. 31-36.

16. Skripnichenko Yu. P., Piatayeva S. V., Volodina M. A., Tsvirkun D. V., Baranov I. I., Vysohkykh M. Yu. Peculiarities of the course of oxidative-reduced reactions in the blood of women with physiological and complicated pregnancy // Ibid. - 2017. - № 8. - P. 60 - 66.