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CHANGES IN MARKERS OF ENDOTHELIAL FUNCTION, LIPID PEROXIDATION AND ANTIOXIDANT PROTECTION IN PREGNANT WOMEN WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Summary

Introduction. *Increasing prevalence of chronic obstructive pulmonary diseases (COPD) in the female population requires timely diagnosis of COPD in pregnant women. Changes in markers of lipid peroxidation and antioxidant protection, which eventually lead to endothelial dysfunction, play a prominent role in pathophysiology of COPD disorders. During pregnancy, these changes cause obstetric and perinatal complications.*

The aim of our study *was to determine the effect of markers of endothelial dysfunction, lipid peroxidation and antioxidant protection on the development of obstetric and perinatal complications in pregnant women with chronic obstructive pulmonary disease of different severity.*

Materials and methods. *Fifty-six pregnant women with clinically and instrumentally verified signs of COPD were examined. The main group of pregnant women was divided into the IA subgroup (29 women with mild bronchial obstruction) and the IB subgroup (27 women with moderate bronchial obstruction). The control group consisted of 24 healthy pregnant women. The function of biochemical markers of endothelial function (endothelin-1 and circulating desquamated endotheliocytes) and the activity of lipid peroxidation and antioxidant protection (malondialdehyde, diene conjugates, superoxide dismutase) were assessed in all groups of women. The incidence of obstetric and perinatal complications in the examined groups of pregnant women with COPD was determined.*

Results and discussion. *In pregnant women with signs of COPD there was a pronounced tendency for the levels of intermediate products of lipid peroxidation to increase (malondialdehyde was 22.6% higher in the IA subgroup and 52.9% higher in the IB subgroup, The study group showed a marked tendency toward an increase in the levels of lipid peroxidation intermediates (malondialdehyde increased in the IA and IS subgroups by 22.6% and 21.9%, respectively, compared with controls) and a decrease in the enzymatic activity of the antioxidant protection system (superoxide dismutase decreased by 15.9% and 21.2% in the IA and IB subgroups, respectively, compared with controls).*

As a result of the imbalance in the LPO/AOP system and the development of endothelial dysfunction, we observed an increase in the development of obstetric and perinatal complications in pregnant women of the main group who had COPD. Anemia (41.4% in the IA and 63.2% in the IB subgroup), placental dysfunction (51.7% in the IA and 66.6% in the IB subgroup), preterm birth threat (13.8% and 25.9%, respectively), and fetal growth retardation syndrome (13.8% and 22.2%, respectively) were more common.

Conclusions. *Pregnant women with COPD have abnormalities in basic markers of endothelial function, lipid peroxidation and antioxidant protection, which are accompanied by an increased incidence of obstetric and perinatal complications and require the development of adequate treatment and prophylaxis programs in pregnant women with COPD.*

Key words: *Pregnancy; Chronic Obstructive Pulmonary Disease; Endothelial Dysfunction; Obstetric Complications; Lipid Peroxidation.*

Introduction

The study of clinical and pathogenetic features of chronic obstructive pulmonary disease and its impact on the course of pregnancy is an important area of research. According to WHO (2021), the incidence of COPD has increased to 600 million cases per year over the last 5 years, with 61% more women being diagnosed with this pathology [1,2]. In turn, the course of pregnancy in women with COPD is associated with a significant increase in obstetric and perinatal morbidity [3]. Thus, according to L. Tamási, I. Horváth in pregnant women with chronic lung pathology, the incidence of complications during pregnancy increases from 3.7% to 8.4% [4]. Such research data serve as the basis for in-depth study of the basic pathophysiological mechanisms of the effect of bronchial obstruction on the work of the main homeostasis systems of the body. In COPD due to excessive mucus production along the airways, air circulation is restricted. It causes lung hyperinflation and gas exchange disorders, which leads to hypoxemia development that is one of the factors of hypoxia development [5]. Chronic bronchial obstruction in COPD accompanied by chronic hypoxia leads to imbalance in oxidant-antioxidant system and contributes to vascular endothelium damage by excessive oxidation products with the development of endothelial dysfunction [6,7]. The antioxidant protection system (AOP), which is responsible for the regulation of lipid peroxidation (LPO) processes, is unable, under the active influence of risk factors, to protect the body from the toxic effects of a large number of formed free radicals. In turn, such COPD risk factors as active and/or passive smoking activate certain endogenous mechanisms: accumulation of neutrophils and macrophages at the level of small vessels in the lungs, which as a result further increases oxidative stress in the body [8,9].

It is known that endothelial dysfunction occurs due to exogenous or endogenous lesions that cause disturbances in the basic regulatory mechanisms of the endothelium, the main task of which is to ensure the optimal course of all endothelium-dependent processes. These include the production of vasodilatory, antiproliferative, angioprotective substances, as well as the regulation of the level of vasoconstrictors, proliferative and thrombotic factors. Chronic systemic low-intensity inflammatory

process, oxidative stress and chronic hypoxia, which are characteristic features of bronchial obstruction in chronic obstructive pulmonary disease (COPD), underlie endothelial dysfunction. A special role in this case belongs to the increase of endothelin-1 concentration in blood as one of the key markers of endothelial dysfunction [10-12].

Assessment of COPD course severity is usually performed with regard to clinical symptoms, the degree of bronchial obstruction and response to bronchodilators. Already after 2-3 years of the disease during COPD there is a structural rearrangement of bronchial tree and pulmonary vessels, which affects pulmonary hemodynamics [13,14]. Even earlier in pulmonary vessels, endothelial cells modulate vascular tone depending on partial O2 level and blood flow changes. Disturbance of this balance in COPD is the cause of vascular disorders already in the initial stages of the disease, which during pregnancy can contribute to the occurrence of obstetric complications such as preeclampsia, placental dysfunction, fetal growth retardation syndrome [15-17].

Therefore, it is important to establish the role of oxidative stress and endothelial dysfunction in the development of obstetric and perinatal complications of the mother and fetus. At the same time, the pathophysiological mechanisms of the development of obstetric pathology as a consequence of endothelial dysfunction in pregnant women with COPD remain largely unexplained, despite the sufficient number of studies. Studying changes in markers of endothelial dysfunction, lipid peroxidation and antioxidant protection in pregnant women with COPD will allow the development of a program to predict the development of obstetric and perinatal complications and determine adequate methods of prevention.

The aim of our study was to determine the effect of markers of endothelial dysfunction, lipid peroxidation and antioxidant protection on the development of obstetric and perinatal complications in pregnant women with chronic obstructive pulmonary disease of different severity.

Materials and Methods

Fifty-six pregnant women with clinically and instrumentally verified signs of COPD were examined. A control group consisted of 24 healthy pregnant women without pathological disorders of the respiratory system. The women's ages ranged from 23 to 35 years. All the pregnant women were inpatients at the department of extragenital pathology of pregnant women of the Ternopil Regional Clinical Perinatal Center "Mother and Child" of the Ternopil Regional Council.

The diagnosis of chronic obstructive pulmonary disease was made in pregnant women with chronic bronchitis, emphysema, bronchial asthma, and bronchiectatic disease, which were established according to the Global Strategy for Asthma Management and Prevention GINA 2021, the adapted evidence-based clinical guidelines "Chronic Obstructive Pulmonary Disease" (2020), the unified clinical protocol for primary, secondary (specialized), tertiary (highly-specialized) medical care, June 27, 2013 No 555 "Chronic obstructive pulmonary disease" and the order of the Ministry of Health Care, October 08, 2013 No 868 "Bronchial asthma"), based on the data of anamnesis, clinical and instrumental examination [18-21].

Criteria for inclusion of patients in the study were clinical, laboratory signs, history data and instrumental methods of examination, corresponding to the diagnosis of chronic obstructive pulmonary disease with I and II degrees of bronchial obstruction.

The exclusion criteria in this study were the presence of extragenital pathology, which may cause similar obstetric and perinatal complications, in particular COPD with degree III and IV bronchial obstruction, arterial hypertension, kidney diseases, diabetes mellitus type 1 and 2, thrombotic complications, systemic connective tissue diseases, digestive diseases. All patients signed an informed consent to participate in the study.

All pregnant women with chronic obstructive pulmonary disease were divided into 2 subgroups depending on the severity of obstructive syndrome in COPD. The degree of severity was determined on the basis of spirometric classification by postbronchodilatation FEF1 (forced expiratory flow in 1 second). The IA group included 29 pregnant women with an FEF1≥80% of the appropriate value, corresponding to a mild degree of bronchial obstruction according to ATS/ERS (2015). The IB group included 27 pregnant women with an FEF1 of 50-79, corresponding to a moderate stage of bronchial obstruction. The FEF1/FVC ratio in both groups was ≤ 0.7 [22].

Assessment of the function of biochemical endothelial markers was performed by determining the plasma concentration of endothelin-1 and the number of desquamated endotheliocytes. Endothelin-1 content in blood plasma was determined by enzyme immunoassay using reagents of Biomedica Medizinprodukte GmbH and Co KG (Austria). The number of circulating desquamated endotheliocytes in blood was determined by Hladovec J. method modified by Petrishchev N.N. et al. [23].

The activity of lipid peroxidation and antioxidant protection was assessed by determining the concentration of malondialdehyde, glutathione, diene conjugates, catalase and superoxide dismutase in blood plasma according to standard methods.

Statistical analysis of the results was performed using Statistica 10.0 (StatSoft, Inc., USA) and Microsoft Office Excel 2010. Mean values (M) and standard errors (m) were also calculated. Significance of differences between mean values was determined using Student's test and t-criterion for dependent and independent samples. Critical level of error probability (p) for checking statistical data was taken to be greater than or equal to 95% (p≤0,05).

Results and discussion

All pregnant women were residents of the Ternopil region and belonged to the Caucasian race. No differences regarding upbringing, age and education were found when comparing the indicators. Height and weight indices were also comparable in all groups of pregnant women. Analysis of the questionnaire showed that the mean age of the patients in group

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IA was 28.1 ± 1.5 years, that of the pregnant women in group IB was 27.5 ± 1.3 years, and that of the control group 26.4 ± 1.7 years. After the survey, we learned that duration of COPD in pregnant women in group IA was 8.1 ± 1.9 years, and in group IB 9.6 ± 2.2 years. Twenty-six (46.4%) women had their first pregnancy, 23 (41.1%) had their second, and 7 (12.5%) had their third or more.

The increase in LPO indices was directly proportional to the duration of obstructive chronic pulmonary disease. This can be explained by the depletion of the basic protective mechanisms against the background of pregnancy. As can be seen from Table 1, the level of malondialdehyde in subgroup IA was 22.6% higher, while in subgroup IB its level increased by 52.9% ($p \leq 0.05$). Diene conjugates were slightly elevated by 7.1% in subgroup IA with mild bronchial obstruction, but in the subgroup with moderate bronchial obstruction their level was already significantly higher by 12.1% (19.77±0.17 versus 16.71±0.16) ($p \leq 0.05$).

Table 1.

LPO/AOP indices in pregnant women with COPD of different severity level

LPO/AOP indices	Subgroup IA (n=29)	Subgroup IB (n=27)	Control (n=24)
MDA, μmol/l	3,58±0,26*	5,88±0,19*	2,77±0,38
DC, μmol/l	17,96±0,35	19,77±0,17*	16,71±0,16
SOD, unit/1ml erythr	54,86±4,45*	51,45±3,97*	65,29±3,59
Catalase, Cat. count	26,57±0,79	24,11±0,39*	27,32±0,93
Glutathion, mol/l	0,65±0,08*	0,46±0,04*	1,34±0,18

Note - the data are reliable in comparison with the control group (p≤0,05)*

In contrast to the increase in LPO indices, the main indicators of antioxidant protection decreased, indicating increased oxidative stress of the whole body in pregnant women with COPD. The main AOP enzyme, superoxide dismutase, decreased by 15.9% and 21.2% in the IA and IB subgroups, respectively, as compared to controls. There was also an 11.7% decrease in catalase levels in IB subgroup compared with control (27.32±0.93 cc vs. 24.110.39 cc). Glutathione levels were significantly lower in both subgroups of pregnant women with COPD (2.1-fold lower in subgroup IA and 2.9-fold lower in subgroup IB) ($p \leq 0.05$).

Elevated levels of major markers of endothelial dysfunction in pregnant women with COPD may be an early marker of obstetric and perinatal complications. Analysis of the endothelial functional status indices obtained in the group of pregnant women with COPD revealed a significant increase in endothelin-1 and the number of circulating desquamated endotheliocytes in all subgroups. Thus, pregnant women with a mild degree of bronchial obstruction had a 2.3-fold higher endothelin-1 level compared with controls, and pregnant women with a moderate degree of bronchial obstruction had a 2.9-fold higher level ($p \leq 0.05$). Serum levels of circulating desquamated endotheliocytes were significantly different in the subgroup of pregnant women with a moderate degree of bronchial obstruction and were 2.7-fold higher than controls (15.58±1.32 x 104/l versus 5.77±1.37 x 104/l), ($p \leq 0.05$). In the subgroup with a mild degree of bronchial obstruction, there was also a 41.1% significant increase in the index of circulating desquamated endotheliocytes compared to controls (9.81±1.26 x 104/l in the IA subgroup versus 5.77±1.37 x 104/l in the control group).

Table 2.

Endothelial functional status indices in the serum of pregnant women with COPD of different severity

Groups of pregnant women	Endothelin-1, fmol/l	Amount of circulating desquamated endotheliocytes, 104 /l
IA subgroup (n=29)	0,118 ± 0,069*	9,81 ± 1,26*
IB subgroup (n=27)	0,146 ± 0,086*	15,58 ± 1,32**
Control (n=24)	0,051 ± 0,021	5,77 ± 1,37

Note - the data are reliable in comparison with the control group (p≤0,05)*

These abnormalities, both in endothelial function and in the LPO/AOP system, may be the basis for the development of obstetric and perinatal complications in the studied groups of patients. We analyzed obstetric and perinatal complications in the main group of pregnant women with COPD and found a 41.4% and 63.2% increase in the frequency of anemia in the IA and IB subgroups, which were 2 and 3 times greater than those in the control group, respectively. The most frequent pathology among obstetric complications was placental dysfunction (in 51.7% in IA and 66.6% in IB subgroups versus 25.0% in controls), which was 2.1 and 2.7 times more frequent compared to controls, respectively. Obviously, with placental dysfunction, irreversible morphological changes in the placental tissue occur as a result of impaired blood circulation in the mother-placenta-fetus system, which negatively affect fetal development and growth and reduce the exchange of nutrients and oxygen between the mother and fetus. As a consequence, fetal growth retardation syndrome was found to be 1.7 and 2.7 times more common in pregnant women in the study group, respectively (13.8% in the IA and 22.2% in the IB subgroups versus 8.3% in controls). Fetal distress during pregnancy was also detected in the study group, whereas no such complication was observed in healthy pregnant women (3.4% in the IA and 7.4% in

the IB subgroups, respectively). Preeclampsia developed 2.7-fold more frequently in pregnant women with a moderate degree of bronchial obstruction compared to those without COPD (22.2% versus 8.3% of controls). It is noteworthy that pregnant women with manifestations of COPD have an increased incidence of the threat of preterm birth. Thus, in the subgroup with a moderate degree of bronchial obstruction, the threat of preterm birth was detected in 7 (25.9%) pregnant women (8.3% in controls), and in 5 (18.5%) of them the pregnancy ended in preterm birth, which was 60% more frequent compared to controls (18.5% vs. 8.3%, respectively). Preterm membranes rupture (PMR) was observed in 2 (6.9%) women in subgroup IA and in 3 (11.1%) women in IB, while in pregnant women without respiratory diseases only one (4.2%) patient had this complication.

Table 3.

Frequency of obstetric and perinatal complications in the study groups of pregnant women with COPD (abs., %)

Index	IA subgroup (n=29)		IB subgroup (n=27)		Controls (n=24)	
	Abs.	%	Abs.	%	Abs.	%
Anemia	12	41,4*	17	63,2*	5	20,8
Threat of preterm birth	4	13,8	7	25,9*	2	8,3
Preeclampsia	3	10,3	6	22,2*	2	8,3
Placental dysfunction	15	51,7*	18	66,6*	6	25,0
Fetal growth retardation syndrome	4	13,8	6	22,2*	2	8,3
Preterm birth	3	10,3	5	18,5*	2	8,3
PMR	2	6,9	3	11,1	1	4,2
Fetal distress in pregnancy	1	3,4	2	7,4*	-	-

Note - the data are reliable in comparison with the control group (p≤0,05)*

Thus, pregnant women with COPD are more likely to have obstetric and perinatal complications, the incidence of which increases in direct proportion to the severity of bronchial obstruction. The development of obstetric and perinatal complications in pregnant women with COPD may be based on a significant imbalance in the LPO/AOP system and the development of endothelial dysfunction. These disorders can be considered as markers of abnormal pregnancy. Early detection of impairments in antioxidant protection and endothelial function in pregnant women with mild to moderate bronchial obstruction will prevent complications. The findings may be useful for the development of adequate treatment programs for possible complications of pregnancy and labor in women with COPD.

Conclusions

1. The increase in the severity of bronchial obstruction in pregnant women with COPD is accompanied by an increase in LPO/AOP intermediates, a decrease in the activity of the main AOP indices in direct proportion to the degree of bronchial obstruction and the development of endothelial dysfunction.

2. An increase in markers of endothelial function, lipid peroxidation, and a decrease in antioxidant protection are accompanied by an increased incidence of obstetric and perinatal complications in pregnant women with COPD. Early detection of impairments in the LPO/AOP system and increased levels of endothelial dysfunction markers in pregnant women with COPD will help to prevent the development of obstetric and perinatal complications in a well-timed manner.

Prospects for further research. Chronic obstructive pulmonary disease in the second half of pregnancy is accompanied by an increased incidence of obstetric and perinatal complications and changes in markers of endothelial function, lipid peroxidation, and antioxidant protection. This requires further research to develop adequate programs for the prevention and timely treatment of these complications.

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ЗМІНИ МАРКЕРІВ ЕНДОТЕЛІАЛЬНОЇ ФУНКЦІЇ, ПЕРОКСИДНОГО ОКИСНЕННЯ ЛІПІДІВ ТА АНТИОКСИДАНТНОГО ЗАХИСТУ У ВАГІТНИХ ІЗ ХРОНІЧНИМ ОБСТРУКТИВНИМ ЗАХВОРЮВАННЯМ ЛЕГЕНЬ

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Резюме

Вступ. Збільшення поширеності хронічних обструктивних захворювань легень (ХОЗЛ) серед жіночого населення потребує своєчасної діагностики ХОЗЛ у вагітних жінок. Не останню роль в патофізіології порушень при ХОЗЛ відіграють зміни маркерів перекисного окиснення ліпідів та антиоксидантного захисту, які з часом призводять до порушень функції ендотелію. Під час вагітності дані зміни стають причиною виникнення різноманітних акушерських та перинатальних ускладнень.

Метою дослідження було встановити вплив маркерів ендотеліальної дисфункції, пероксидного окиснення ліпідів та антиоксидантного захисту на розвиток акушерських та перинатальних ускладнень у вагітних з хронічним обструктивним захворюванням легень різного ступеня важкості.

Матеріал та методи дослідження. Обстежено 56 вагітних жінок з клінічно та інструментально верифікованими ознаками ХОЗЛ. Основну групу вагітних було розподілено на ІА підгрупу (29 жінок з легким ступенем бронхообструкції) та ІВ підгрупу (27 жінок з помірним ступенем бронхообструкції). Контрольну групу склали 24 здорових вагітних. У всіх групах жінок було проведено оцінку функції біохімічних маркерів ендотелію (ендотелін-1 та циркулюючі десквамовані ендотеліоцити) та оцінку активності процесів перекисного окиснення ліпідів та антиоксидантного захисту (малоновий діальдегід, дієнові кон'югати, супероксиддисмутаза, каталаза, глутатіон). Встановлено частоту розвитку акушерських та перинатальних ускладнень у групах вагітних із ХОЗЛ, що обстежувалися.

Результати дослідження. При обстеженні вагітних із ознаками ХОЗЛ спостерігалася виражена тенденція до підвищення рівня проміжних продуктів перекисного окиснення ліпідів (малоновий диальдегід у ІА підгрупі більший на 22,6%, у ІВ підгрупі на 52,9%), та зниження ферментної активності системи антиоксидантного захисту (у ІА та ІВ підгрупах супероксиддисмутаза зменшувалася порівняно з контролем відповідно на 15,9% та 21,2%), розвиток ендотеліальної дисфункції (ендотелін-1 у 2,3 рази в ІА підгрупі та у вагітних ІВ підгрупи у 2,9 рази вищий порівняно з контролем).

Внаслідок порушень балансу в системі ПОЛ/АОЗ та розвитку ендотеліальної дисфункції нами було відмічено зростання розвитку акушерських та перинатальних ускладнень у вагітних основної групи, що мали ХОЗЛ. Найчастіше мали місце анемія (41,4% в ІА та 63,2% в ІВ підгрупі), дисфункція плаценти (51,7% в ІА та 66,6 % в ІВ підгрупі), загроза передчасних пологів (13,8% та 25,9% відповідно) та синдром затримки росту плода (13,8% та 22,2% відповідно).

Висновки. У вагітних жінок з ХОЗЛ спостерігається порушення основних маркерів ендотеліальної функції, перекисного окиснення ліпідів та антиоксидантного захисту яке супроводжується збільшенням частоти акушерських та перинатальних ускладнень, що потребує розробки адекватних програм лікування та профілактики у вагітних із ХОЗЛ.

Ключові слова: вагітність; хронічне обструктивне захворювання легень; ендотеліальна дисфункція; акушерські ускладнення; перекисне окиснення ліпідів.

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