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# THE FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE INFLUENCE ON THE PREGNANCY COMPLICATIONS DEVELOPMENT

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## ABSTRACT

In recent years, the prevalence of chronic obstructive pulmonary disease (COPD) has been increasingly observed among women, which is one of the reasons for the higher interest of scientists in the influence of COPD on pregnant woman.

**The aim of our study** was to establish the features of the development pregnancy complications in pregnant women with COPD.

**Materials and methods.** 77 pregnant women with clinically and instrumentally verified signs of COPD were examined and were divided into 2 subgroups depending on the degree of bronchial obstruction: IA - 43 pregnant women with FEV1 $\geq$ 80%, IB - 34 pregnant women with FEV1 50-79%. The control group consisted of 27 healthy pregnant women. The cytokine profile was determined and a correlational interaction with the degree of bronchial obstruction and the frequency of obstetric and perinatal complications was established.

**The results.** Our analysis of cytokine profile indicators in pregnant women with chronic obstructive pulmonary disease at the stage of mild and moderate bronchial obstruction showed a characteristic and reliable increase in the level of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6) and a simultaneous decrease in the level of anti-inflammatory IL-10 ( $p\leq 0.05$ ).

We established that an increase in the degree of bronchial obstruction is also associated with a higher frequency of detection of such pregnancy and childbirth complications as anemia, respectively, by 3.1 times, the threatened of premature birth by 9 times, preeclampsia by 7 times, placental dysfunction by 3.4 times, intrauterine growth restriction 8 times, premature birth 3.5 times, premature rupture of membranes during labor 4 times, and fetal distress 3 times higher compared to the control group.

**Conclusions.** COPD in pregnant women is characterized by systemic disturbances in the cytokine balance and is accompanied by a significant increase in the frequency of obstetric and perinatal complications, the frequency of which depends on the degree of bronchial obstruction.

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### **Introduction.**

The development and progression of chronic obstructive pulmonary disease during pregnancy and its impact on the development of obstetric and perinatal complications is an urgent problem in obstetrics. In recent years, the prevalence of this lung disease has tended to increase, especially among young women of reproductive age, due to the influence of such risk factors as smoking, living in polluted areas, etc. [1,2,3,4,5]. Thus, according to L. Tamási, I. Horváth (2011), the frequency of complications during pregnancy increases from 3.7% to 8.4% in pregnant women with chronic lung pathology [6]. Such data serve as a basis for an in-depth study of the pathophysiological processes underlying the development of disease complications in COPD. In the pathogenesis of COPD, the opening in the lungs, which develops under the negative influence of harmful particles and gases, plays a key role [7,8]. Although the main site of the inflammatory process in the lungs is the small airways, and it can often be present in the large bronchi, lung parenchyma, or pulmonary vessels, in COPD, markers of the peripheral blood level often increase, which indicate an increase of systemic inflammatory response and has a negative impact on the development of pregnancy complications [9,10].

The basis of the systemic inflammatory reaction is the launch of a cytokine cascade, which includes pro-inflammatory cytokines on the one hand, and anti-inflammatory cytokines on the other. The human organism doesn't have a constant level of cytokines, the production of them is regulated under the influence of a harmful factor at the level of gene transcription [11]. The balance between these groups of mediators affects the course and outcome of the pregnancy, and in the presence of a pathological process, control over the processes of proliferation, cell differentiation, and programmed cell death is disrupted [11]. In the pathogenesis of COPD, cytokines IL-1 $\beta$ , IL-6, IL-8, IL-10, and TNF- $\alpha$  play the main role [12,13,14]. Their functions during the initiation of the pathological inflammatory process include activation of leukocytes and endothelial cells, increase in cytotoxicity of phagocytes and adhesive properties of leukocytes. These changes in the pregnant woman's body, in turn, cause pathological disorders in the placental tissue, which is the main protective barrier during pregnancy [15]. Thus, chronic inflammatory processes in the placenta can cause such obstetric and perinatal complications as preeclampsia, placental dysfunction, the threatened of premature birth, intrauterine growth restriction, etc. [16,17,18,19].

At the same time, the pathophysiological mechanisms of the development of obstetric pathology, as a result of systemic inflammation in pregnant women with COPD, remain largely unexplained despite a sufficiently large number of scientific studies. Establishing changes in markers of systemic inflammation in the development of obstetric and perinatal complications in pregnant women with COPD will help to develop a pathogenetically based program for the treatment of complications and to determine adequate methods of their prevention.

**The aim of our study** was to establish the features of the development pregnancy complications in pregnant women with COPD.

### **Materials and methods.**

Seventy-seven pregnant women with clinically and instrumentally verified signs of COPD were examined. A control group consisted of 27 healthy pregnant women without pathological disorders of the respiratory system. The women's ages ranged from 22 to 37 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 during 2019-2022.

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 the obstructive syndrome in COPD.

The concentration of cytokines IL-1 $\beta$ , IL-6, IL-10 was quantitatively determined by the enzyme-linked immunosorbent assay method on a Stat Fax 303 strip analyzer (Awareness Technology

Inc., USA) with test systems. Examination of all patients was performed in the period of 28-30 weeks of pregnancy. Statistical analysis of the results was performed using Statistica 10.0 (StatSoft, Inc., USA) and Microsoft Office Excel 2010 programs. 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. A difference of  $p < 0.05$  was considered significant. The Pearson correlation method was used to assess the correlation using Microsoft Excel 2010.

### Results and discussion.

According to the data we received, all pregnant women were residents of the Ternopil region and belonged to the Caucasian race. Growth and weight indicators were comparable in all groups of pregnant women. All patients voluntarily agreed to participate in the study. It is known that the duration of COPD in pregnant women of group IA was  $8.3 \pm 1.7$  years, in group IB -  $9.7 \pm 2.3$  years. There was no statistical difference between the groups of examined women by age ( $p > 0.05$ ). Thus, the average age of patients in group IA was  $27.1 \pm 1.5$  years, pregnant women in group IB -  $29.8 \pm 1.5$  years, control group  $26.8 \pm 1.7$  years. After the examination we have known that for 49 (47.1%) women it was the first pregnancy, for 42 (40.4%) the second, and for 13 (12.5%) the third or more.

In the course of the study, we analyzed the levels of pro-inflammatory (IL-1 $\beta$ , IL-6) and anti-inflammatory (IL-10) mediators of inflammation in pregnant women with COPD with a mild and moderate degree of bronchial obstruction. At the same time, IL-1 $\beta$  concentration showed a significant increase in subgroups of pregnant women with mild and moderate degree of bronchial obstruction. Thus, compared to the control group, where there were healthy pregnant women, the level of IL-1 $\beta$  was 1.8 times higher in the IA and 2.1 times higher in the IB subgroup. An increase in IL-1 $\beta$  may be the basis for the occurrence of obstetric and perinatal complications, which is comparable to the data of Khong, Y.T. (2015), who established that IL-1 $\beta$  during pregnancy in response to the presence of an infectious process in the body causes systemic and local changes in the chorion and, subsequently, the placenta [20]. Also, in the IB subgroup, a statistically significant increase in the systemic level of IL-6, which is the leading marker of inflammation activation during pregnancy, was observed in the IA and IB subgroups by 1.5 and 1.8 times, respectively, compared to the control group.

During the physiological course of pregnancy, as is known, there is relative immunosuppression in the body, which is manifested at the level of cytokine balance by the dominance of anti-inflammatory IL-10. It provides local immunosuppression by limiting the activity of normal killers, macrophages, expression of steroid hormone receptors. As demonstrated by the analysis of the results of the level of IL-10 in blood serum, its decrease was reliable in the main group of pregnant women compared to the control (1.3 times less in the IA and 1.7 times in the IB subgroups). A decrease in the concentration of IL-10 indicates a disruption of the cytokine balance towards pro-inflammatory reactions at the local and general levels, which can also become the basis for the occurrence of obstetric and perinatal complications in the group of pregnant women with COPD.

The study of the results of the level of inflammatory mediators in pregnant women with COPD revealed reliable shifts in the regulation of the cytokine profile in all subgroups of examined pregnant women, which indicates a decrease in cellular immunity and the beginning of an inflammatory reaction at the systemic level. At the same time, the detected cytokine level violations were directly proportionally correlated with the degree of broncho-obstruction. Thus, in the main group of pregnant women with COPD, a reliable inverse relationship of strong and moderate strength was found between the degree of bronchial obstruction and the level of IL-1 $\beta$ . In the IA subgroup with a mild degree of bronchial obstruction ( $FEV_1 \geq 80\%$ ),  $r = -0.81$  ( $p < 0.05$ ), in the IB subgroup with a moderate degree of bronchial obstruction ( $FEV_1 50-79\%$ )  $r = -0.67$ ; ( $p < 0.05$ ) (Fig. 1). Similar results were recorded among examined women with COPD, where there is a reliable inverse strong correlation between the degree of bronchial obstruction and the IL-6 index. In the IA subgroup ( $FEV_1 \geq 80\%$ )  $r = -0.88$  ( $p < 0.05$ ), in the IB subgroup ( $FEV_1 50-79\%$ )  $r = -0.78$ ; ( $p < 0.05$ ) (Fig. 2)

Correlation analysis showed that an increase in the degree of bronchial obstruction in pregnant women was accompanied by a directly proportional increase in the level of IL-10: in the subgroup of women with a mild degree of bronchial obstruction ( $FEV_1 \geq 80\%$ ),  $r = 0.80$ ; ( $p < 0.05$ ), in the group of women with a moderate degree of bronchial obstruction ( $FEV_1 50-79\%$ )  $r = 0.86$ ; (Fig. 3).

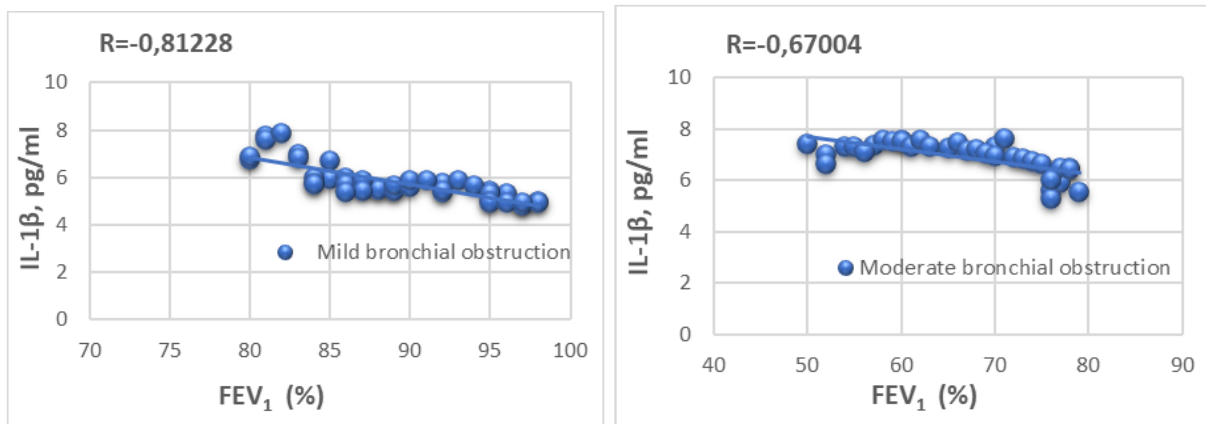


Fig. 1 Analysis of the correlation between the degree of bronchial obstruction and IL-1β indicator in pregnant women with COPD.

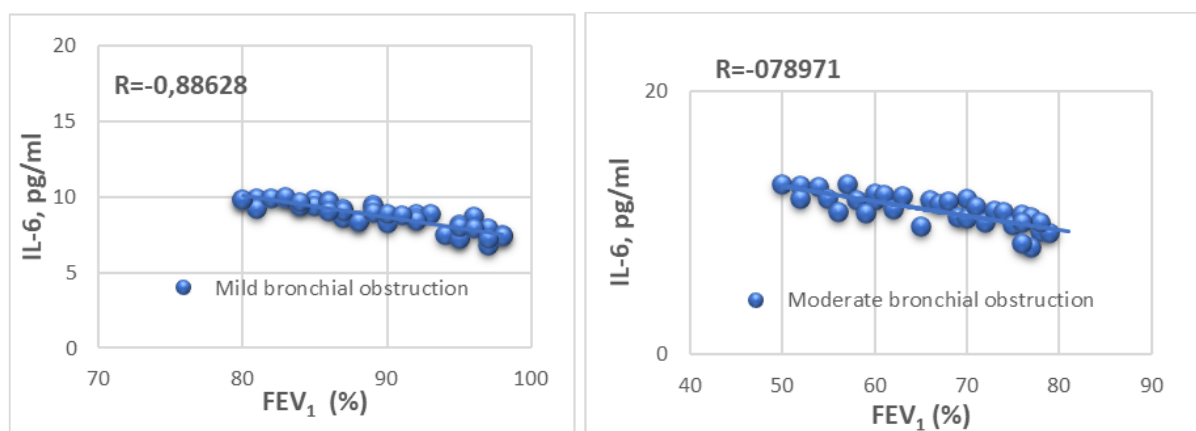


Fig. 2 Analysis of the correlation between the degree of bronchial obstruction and the IL-6 index in pregnant women with COPD.

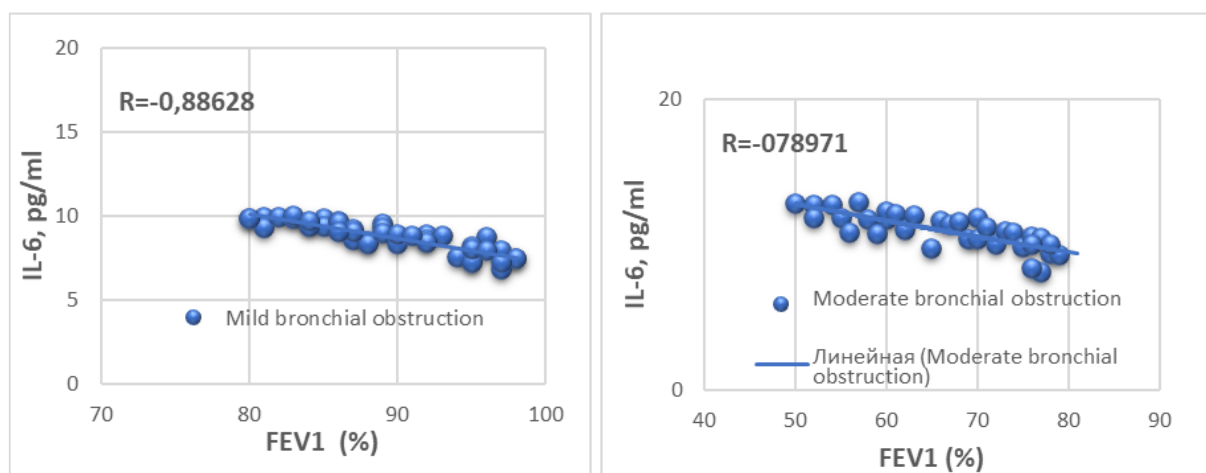


Fig. 3 Analysis of the correlation between the degree of bronchial obstruction and the IL-10 index in pregnant women with COPD

We analyzed obstetric and perinatal complications in the main group of pregnant women with COPD (Table 1) and found an increase in the frequency of anemia by 41.9% in the IA and by 64.7% in the IB subgroup, which is 3.7 and 5.8, respectively times more than in the control. The most common pathology among obstetric complications was placental dysfunction, which was found in 51.1% of the



IA and 70.5% of the IB subgroups, against 25.9% in the control group, which is 1.9 and 2.7 times more frequent, respectively compared to control. It is obvious that with placental dysfunction, as a result of impaired blood circulation in the mother-placenta-fetus system, irreversible morphological changes occur in the placental tissue, which have a negative impact on the development and growth of the fetus and reduce the exchange of nutrients and oxygen between the mother and the fetus. As a result, intrauterine growth restriction was detected in pregnant women from the main group (11.6% in the IA and 23.5% in the IB subgroup), in contrast to the control group of healthy pregnant women, where this pathology was not detected. Also, in the main group, the development of fetal distress during pregnancy was established (respectively, 2.3% in the IA and 8.8% in the IB subgroup), while no such complication was observed in healthy pregnant women. As a result of chronic hypoxic injury, pregnant women with COPD often experience anemia during pregnancy. In the IA and IB subgroups, anemia was diagnosed 6.0 and 7.3 times more often compared to the control group. Pregnant women with a moderate degree of bronchial obstruction developed preeclampsia 2.2 times more often compared to pregnant women in the subgroup with a mild degree of bronchial obstruction (20.5% vs. 9.3%, respectively). It is noteworthy that the frequency of the threat of premature birth increases in pregnant women with COPD manifestations. Thus, in the subgroup with a moderate degree of broncho-obstruction, the threat of premature birth was detected in 9 (26.4%) pregnant women (3.7% in controls), and of them, 7 (17.6%) pregnancies ended in premature birth. In the subgroup with a mild degree of bronchial obstruction, the threat of premature birth occurred in 6 women (13.9%), four (11.6%) of whom later had premature birth. No cases of premature birth were observed in the control group. During childbirth, premature rupture of the membranes occurred in 3 (6.9%) parturients from the IA subgroup and in 4 (11.7%) women from the IB subgroup, while in pregnant women without respiratory tract diseases only one patient this complication was noted (3.7%).

Therefore, pregnant women with COPD are significantly more likely to develop obstetric and perinatal complications, which depend on the degree of bronchial obstruction.

Table 1. Frequency of obstetric and perinatal complications in the study groups of pregnant women with COPD (abs., %)

Index	IA subgroup (n=43)		IB subgroup (n=34)		Control group (n=27)	
	Abs.	%	Abs.	%	Abs.	%
Placental dysfunction	22	51,1	24	70,5	7	25,9
Intrauterine growth restriction	5	11,6	8	23,5	-	-
Fetal distress in pregnancy	1	2,3	3	8,8	-	-
Anemia	18	41,9	22	64,7	3	11,1
Preeclampsia	4	9,3	7	20,5	-	-
Threatened of pretem birth	6	13,9	9	26,4	1	3,7
Preterm delivery	4	9,3	7	17,6	2	7,4
Premature rupture of membrane	3	6,9	4	11,7	1	3,7

### Discussion.

Our analysis of cytokine profile indicators in pregnant women with chronic obstructive pulmonary disease at the stage of mild and moderate bronchial obstruction showed a characteristic and reliable increase in the level of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6) and a simultaneous decrease in the level of anti-inflammatory IL-10 ( $p \leq 0.05$ ). Dysregulation of the inflammatory response in COPD in pregnant women became the main basis for the development of obstetric and perinatal complications.

We established that an increase in the degree of bronchial obstruction is also associated with a higher frequency of detection of such pregnancy and childbirth complications as anemia, respectively,

by 3.1 times, the threat of premature birth by 9 times, preeclampsia by 7 times, placental dysfunction by 3.4 times, growth retardation syndrome of the fetus 8 times, premature birth 3.5 times, premature rupture of membranes during labor 4 times, and fetal distress 3 times. With correlations help it was established that the basis for the development of these complications is chronic hypoxia and the inflammatory process, which was manifested not only by an imbalance of interleukins in the form of an increase in the levels of IL-1 $\beta$ , IL-6 and a decrease in the level of IL-10, but also an inverse correlation was established between FEV1 level and IL-1 $\beta$  level ( $rI = -0.81$ ,  $rII = -0.67$   $p < 0.01$ ), FEV1 and IL-6 ( $rI = -0.88$ ,  $rII = -0.78$ ,  $p < 0.01$ ), and a direct correlation between FEV1 and IL-10 ( $rI = 0.80$ ,  $rII = 0.86$ ,  $p < 0.01$ ).

Thus, COPD in pregnant women is characterized by systemic disturbances in the cytokine balance and is accompanied by a significant increase in the frequency of obstetric and perinatal complications, the frequency of which depends on the degree of bronchial obstruction and requires the development of a pathogenetically based treatment for such pregnant women.

### Conclusions.

In pregnant women with COPD, an increase in the level of pro-inflammatory cytokines - IL-1 $\beta$  ( $rI = -0.81$ ,  $rII = -0.67$ ), IL-6 ( $rI = -0.88$ ,  $rII = -0.78$ ) and the inversely proportional level of anti-inflammatory IL-10 ( $rI = 0.80$ ,  $rII = 0.86$ ), which can be an early prognostic criterion for the development of obstetric and perinatal complications.

We established that an increase in the degree of broncho-obstruction is also associated with a higher frequency of detection of such complications of pregnancy and childbirth as anemia, respectively, by 3.1 times, the threat of premature birth by 9 times, preeclampsia by 7 times, placental dysfunction by 3.4 times, intrauterine growth restriction 8 times, preterm birth 3.5 times, premature rupture of membranes during labor 4 times, and fetal distress 3 times. The basis for the development of these complications is chronic hypoxia and the inflammatory process, which was manifested not only by an imbalance of interleukins in the form of an increase in the levels of IL-1 $\beta$ , IL-6 and a decrease in the level of IL-10, but also an inverse correlation was established the relationship between the level of FEV1 and the level of IL-1 $\beta$  ( $rI = -0.81$ ,  $rII = -0.67$   $p < 0.01$ ), FEV1 and IL-6 ( $rI = -0.88$ ,  $rII = -0.78$  ,  $p < 0.01$ ), and a direct correlation between FEV1 and IL-10 ( $rI = 0.80$ ,  $rII = 0.86$ ,  $p < 0.01$ ).

Prospects for further scientific research. The results of the study justify the need to develop individual programs for predicting and treating obstetric and perinatal complications for pregnant women with COPD.

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