



CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN WOMEN

Atoeva Muniskhon Nabiyeвна
Bukhara State Medical Institute

Abstract: Chronic obstructive pulmonary disease (COPD) remains a focus of medical science and practice. This article presents a review of the current literature on COPD in women. It presents data on the prevalence of the disease, specific susceptibility to risk factors, age-related aspects of development, progression, outcomes, and clinical manifestations of COPD, as well as differences in response to pharmacotherapy in women and men. Thus, a number of studies have demonstrated a high susceptibility of women to the effects of tobacco smoke, a predisposition to the development of the bronchitis phenotype of COPD, a severe course with frequent exacerbations, and a low risk of death after exacerbations. The results of this review suggest that gender differences can be explained by anatomical differences in the development of the respiratory system and the cyclical hormonal activity of the female body, which manifests itself in greater airway hyperreactivity and, consequently, a higher incidence of severe COPD.

Keywords: chronic obstructive pulmonary disease, women.

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic inflammatory diseases in developed and developing countries [49]. According to experts from the World Health Organization (WHO), there are approximately 210 million people with COPD worldwide. In the Russian Federation (RF), approximately 2.4 million people suffer from this disease. However, according to epidemiological studies, the number is significantly higher, currently reaching 16 million people [24]. The high prevalence of the disease, the predicted steady increase in the number of patients, the increase in hospitalizations, disability, and mortality rates indicate the global nature of the problem of COPD [3]. Consequently, interest in this disease is growing. One of the most complex and poorly studied issues is the issue of gender differences in the development, course and outcomes of COPD. Traditionally, COPD is considered a disease of the second half of life, which occurs predominantly in male smokers [50]. In this regard, the diagnosis is significantly more often made in male smokers than in women (58% versus 42%; $p < 0.05$) [17]. At the same time, modern epidemiological studies indicate a high prevalence of COPD among women, regardless of smoking status [41]. According to epidemiological data, in the USA, Canada, Italy, Sweden and the UK, COPD affects 3 to 15% of women [20]. According to K. Nattori, K. Kida [36], the incidence of COPD among women is 7.3 per 1,000 population, which is slightly different from the incidence of COPD among men - 9.3 per 1,000 population. In addition, the prevalence of COPD in black women (7%) is higher than in white women (5.2%), white men (2.9%), and black men (2.4%) [23]. The incidence of COPD among women is significantly higher in younger age groups (50-60 years) compared to men [9]. Medical practice shows that today the diagnosis of COPD is increasingly being made in both smoking and non-smoking middle-aged women [29]. The presented data indicate a high prevalence of COPD among women and the need to reconsider the view on the priority of COPD diagnosis among older male smokers [46, 47]. Of all the epidemiological indicators related to COPD, mortality is the most informative parameter [22, 33]. According to projections from the Global Burden of Disease Study, COPD, which ranked 6th in the number of deaths in 1990, will move to 3rd place by 2020, and to 4th place among causes of death by 2030 [24]. According to



WHO estimates, 3.17 million people worldwide died from this disease in 2015, which accounted for almost 5% of all deaths that year. Experts note that the mortality rate from COPD is increasing faster than the mortality rate from other diseases and will almost double by the beginning of 2030 [1]. The trend of increasing mortality from COPD is clearly visible in the female population. In the Russian Federation, over the past two decades, this indicator among women over 55 has increased 15-fold, while among men over 75, mortality has increased threefold [2]. Increased mortality among women has also been observed in other countries. For example, in the United States, from 1999 to 2009, mortality from COPD increased by 19% among women and by only 5% among men [8]. In Sweden, mortality from COPD among women has continued to increase since 1999. Moreover, life expectancy among female patients decreased by 9.4 years, and among male patients by 7.4 years compared to individuals without COPD [43]. According to isolated data, mortality from COPD is higher among women than from breast and lung cancer [4]. One of the causes of death in COPD is a severe exacerbation of the disease. A number of studies have examined gender differences in COPD patients in the frequency of exacerbations, hospitalizations, and mortality. In the study by A.V. Gonzales et al. [25], it was found that, with the same level of medical care, COPD exacerbations develop less frequently in women than in men. The authors explain this fact by the fact that women are less likely to seek emergency medical care in case of an exacerbation of the disease. At the same time, some authors note more frequent exacerbations among non-smoking patients with COPD in women, which they explain by the presence of a greater number of comorbidities in them compared to men [27, 34]. However, among women with COPD, the risk of death after an exacerbation of the disease is lower than in men [39]. Similar data were obtained among non-smoking patients with COPD. In women, the risk of death after repeated hospitalizations is lower than in men [27]. According to the epidemiological study National Health and Nutrition Examination Survey (NHANES), the mortality rate among participants in NHANES III decreased by 15.8% for patients with moderate or severe COPD, by 25.2% for patients with mild COPD compared with NHANES I. At the same time, the decrease in mortality among men with moderate or severe COPD (-17.8%) exceeded the change in this indicator among women (+3%) [15]. The high prevalence, combined with increased mortality, frequent exacerbations of COPD with a lower risk of death after exacerbations, determine the relevance of the problem of COPD in women. Despite the enormity of the socioeconomic burden, this problem is far from resolved and requires close attention [46]. In addition to studying the causes of the increased prevalence of COPD among women, it is necessary to investigate the gender characteristics of the disease and susceptibility to risk factors for early diagnosis and timely treatment. The increase in the number of women in the structure of COPD morbidity and mortality is largely due to the global tobacco epidemic, which has led to the widespread use of tobacco smoking among women [5]. It is expected that by 2025 more than 500 million women will be smokers, which will amount to about 20% of the female population of the planet. A study by J. Ancochea et al. [9] found that women with COPD may smoke significantly less compared to men. With the same number of cigarettes smoked, the degree of bronchial obstruction and the severity of COPD in women are higher than in men [21]. A higher susceptibility of women to the development of severe COPD is indicated by a low spirometric indicator of forced expiratory volume in the first second (FEV1) and high severity of the disease with a shorter smoking history and intensity in female patients under 60 years of age [42]. It has also been shown that with a smoking index of less than 20 pack-years, women have a more pronounced airflow limitation (FEV1) compared to men, and with an index of 25 pack-years, there are no gender differences. It is assumed that women's



greater exposure to the harmful effects of tobacco and more severe impairment of lung function may explain, to some extent, the high prevalence of COPD in the female population. A study by Y.I. Kim et al. [28] using high-resolution computed tomography found that smoking women with COPD had greater airway wall thickness and smaller internal airway diameters ($p < 0.001$) compared to men [28]. These data are consistent with the results of other researchers [30]. The authors also found that non-smoking women have a lower FEV1 than non-smoking men, but a significantly higher FEV1 than smoking women. Gender-related differences in respiratory function in non-smokers explain the fact that smoking women develop more severe lung damage than men. At the same time, a study by J. Connett et al. [19] showed that after quitting smoking, women experience better recovery of lung function than men (3.7 and 1.6%, respectively; $p < 0.001$). Smoking in women is the main risk factor for the development of bronchial hyperreactivity, associated with a high risk of progression and mortality from COPD, while in men, such risk factors are considered to be atopy and bronchial asthma. Bronchial hyperreactivity is detected in smoking women with mild to moderate COPD 1.5 times more often than in men [14]. The risk of developing bronchial hyperreactivity increases significantly in women during the reproductive period, which indicates multiple factors contributing to the development of this pathology in the female population. Women are characterized by increased metabolic dysregulation already in the early stages of COPD compared to men [44]. A number of studies have confirmed the proinflammatory contribution of estrogens to obliterating lung lesions in chronic obstructive diseases. Steroid hormones, in particular 17 β -estradiol, act as mitogens in obliterative processes in lung tissue [12]. Estrogens induce proinflammatory cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), which are capable of generating reactive oxygen and nitrogen species that play an important role in the pathogenesis of estrogen-dependent pulmonary diseases [40]. The mitogenic effects of estrogens, along with their potentiating effect on the development of oxidative stress, may contribute to the early development of COPD in women. Due to cyclic hormonal activity, women initially have a higher concentration of proinflammatory interleukin-8 (IL-8). Tobacco smoking, in turn, contributes to an increase in IL-8 levels, which leads to an even greater increase in the content of neutrophils in the airways. This likely explains women's particular sensitivity to the pathological effects of cigarette smoke. Gender differences may also be due to increased metabolism in women under the influence of cigarette smoke due to stimulation of estrogen receptors in lung tissue, production of cytochrome P450, and increased oxidant production [26]. This likely explains women's potentially higher susceptibility to the negative effects of cigarette smoke compared to men. Despite the important role of smoking in the development of COPD in women, it has been noted that smoking is far from the only risk factor, as two-thirds of cases of the disease occur in non-smoking women [41]. A significant role in the incidence of COPD in non-smoking women is played by the influence of external irritants, which trigger abnormal inflammation in the bronchopulmonary system. These factors include not only environmental pollution but also exposure to household air pollutants from cooking and fuel combustion. It is believed that low-income individuals, among whom women predominate, are at higher risk of such exposure [45], especially in Asia and Africa. Data indicate that indoor air pollution from the combustion of coal and biofuels for heating and cooking without proper ventilation causes the death of 2 million women and children annually [24]. The results of the study by Y. Hong et al. [27] showed that non-smoking women and men with COPD exposed to household air pollutants develop various changes in the bronchopulmonary system. Women predominantly develop an inflammatory process in the bronchi, while men develop emphysema.



This is confirmed by computed tomography data. Women, compared to men, have a higher WA% – the ratio of the wall area to the lumen area of the bronchus (71.8 ± 5 versus 69.4 ± 5.3 ; $p = 0.013$) and a lower EI – the emphysema index (3.5 ± 4.2 versus 6.2 ± 5.7 ; $p = 0.01$) with no significant differences in the clinical picture, anamnesis and spirometry parameters [30]. These data suggest that household air pollutants, along with tobacco smoking, are a major risk factor for the development of COPD in women. This should be taken into account in clinical practice to ensure early detection of COPD in both female smokers and non-smokers, as they are susceptible to developing more severe bronchopulmonary lesions [51].

In the past decade, gender-specific differences in symptoms, comorbidities, and treatment response have been actively studied [11, 13, 32]. Population studies PLAT-INO (Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar), ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Endpoints) showed that women with COPD more often complain of shortness of breath, noting more intense dyspnea compared to men with the same degree of respiratory failure and a shorter smoking history [24]. At the same time, women, unlike men, complain significantly less about sputum production, with no significant differences in CAT test results [10, 48]. Researchers tend to explain the difference in complaints by several factors. Firstly, by the different diffusion capacity of the lungs in women and men. Physiologically, women have lower diffusion capacity than men due to their lower muscle mass [51]. Secondly, gender differences in behavioral culture and social roles lead women to report sputum production less frequently [25]. Some researchers believe that women's tendency to complain of shortness of breath is the reason for the more frequent diagnosis of asthma instead of COPD [24]. Gender differences in the structure of comorbidities in COPD have been poorly studied. Epidemiological studies by domestic and foreign researchers note that patients with COPD are predominantly affected by coronary heart disease, heart failure, atrial fibrillation, arterial hypertension, obesity and overweight, depression, osteoporosis, etc. [18, 24]. A few studies have noted that a number of comorbidities are statistically significantly more common in women, significantly impacting quality of life [35]. Unlike men, women have a lower quality of life, which is associated with higher levels of depression and anxiety [6, 38]. Women with COPD report a significant decrease in quality of life already in the early stages of the disease. It has been noted that women with COPD have a lower incidence of cardiovascular diseases (hypertension, myocardial infarction, angina pectoris, and ischemic heart disease), but a higher incidence of osteoporosis, diabetes mellitus, and gastrointestinal diseases [16]. A study by R. Almagro et al. [7] showed that ischemic heart disease and alcoholism were less common among women, but chronic heart failure, osteoporosis, and diabetes mellitus were more common. The presence of gender differences in the structure of comorbid pathology should be taken into account when prescribing pharmacological therapy for COPD, given the side effects of systemic and inhaled steroids [24]. In light of the concept of gender-specific characteristics of COPD, the hypothesis of different responses of male and female patients to therapy for this disease is actively considered [16]. Data on the relationship between gender characteristics and the effectiveness of drug therapy for COPD are contradictory [32, 37]. Some studies have shown that there are no gender differences in the dynamics of the spirometric index FEV1 during combination therapy with beta-adrenergic agonists and inhaled glucocorticosteroids. Other studies have shown a higher effectiveness of glucocorticosteroid therapy in men and a higher frequency of exacerbations in women after discontinuation of inhaled steroids. It can be assumed that the dosage, delivery, and effectiveness of inhaled drugs are associated with gender-specific characteristics of the structure and functioning of the bronchopulmonary system. Large-scale



clinical trials are needed to determine the specific responses to drug therapy in men and women with COPD. Most existing studies have not assessed treatment efficacy in men and women. Furthermore, many randomized clinical trials have included only men with COPD in their protocols [10]. Pulmonary rehabilitation, aimed at reducing the physical and emotional impact of the disease on a person's life, is part of the therapy for patients with COPD. Pulmonary rehabilitation programs include physical exercise combined with information on the most effective ways to maintain one's health, including training in the use of supportive therapy, nutritional recommendations, etc. The positive effect of pulmonary rehabilitation in patients with COPD, regardless of gender, was demonstrated in the study by L.P. Nguyen et al. [37]. At the same time, it was noted that women, after pulmonary rehabilitation, showed a statistically significant improvement in the parameters of the general quality of life according to the St. George's Hospital questionnaire (SGRQ), compared to men ($p = 0.01$). In the study by X. Li et al. [31]. A study showed that women with COPD experienced a twofold improvement in FEV1 (%) after four months of ipratropium bromide maintenance therapy, compared to men. An inverse relationship between the bronchodilator effect and body mass index was observed only in women, while no such relationship was observed in men. Gender-related changes in FEV1 due to ipratropium therapy persisted for 2 years ($p=0.0134$). The study results support the hypothesis of gender differences in sensitivity to pharmacological treatment of COPD.

Conclusion

In conclusion, it should be noted that COPD occurs in women with the same frequency as in men. The main risk factors for COPD in women are tobacco smoking and household air pollutants. Women's high susceptibility to the negative effects of tobacco is due to the anatomical and physiological characteristics of the respiratory system and cyclic hormonal activity. Characteristics of COPD manifestations in women include frequent onset in middle age, frequent complaints of intense shortness of breath, a severe course of the disease with frequent exacerbations and a low risk of death after exacerbations, and a significant decrease in quality of life in the early stages of the disease. It is important to highlight gender-specific differences in response to pharmacotherapy, which is crucial for the search for targeted pharmacological approaches to preventing COPD exacerbations in women. The problem of COPD in women is particularly relevant in light of the WHO program to combat chronic respiratory diseases. Studying the biological and immuno-metabolic mechanisms of COPD development and progression in women will enable the development of gender-specific prevention and treatment strategies, thereby reducing the burden of morbidity, disability, and premature mortality.

LITERATURE

1. Всемирная организация здравоохранения. Десять ведущих причин смерти. 2011. Информационный бюллетень № 310. URL: <https://www.who.int/ru/news-room/factsheets/detail/the-top-10-causes-of-death> (дата обращения 16.10.2018).

Заболеваемость населения старше трудоспособного возраста (с 55 лет у женщин и с 60 лет у мужчин) по России в 2017 году. Статистические материалы. Часть VII. М.: Минздрав России, ФГБУ «ЦНИИОИЗ» Минздрава России, 2018. 183 с. URL: <https://www.ros-minzdrav.ru/ministry/61/22/stranitsa-979/statisticheskie-i-informatsionnye-materialy/statisticheskiy-sbornik-2017-god> (дата обращения 13.11.2018).

1. Кытикова О.Ю., Гвозденко Т.А., Антонюк М.В. Современные аспекты распространенности хронических бронхолегочных заболеваний // Бюллетень физио-



- логии и патологии дыхания. 2017. Вып.64. С.94–100. doi: 10.12737/article_5936346fdcf1f3.32482903
2. Овчаренко С.И., Капустина В.А. Особенности хронической обструктивной болезни легких у женщин
// *Consilium Medicum*. 2009. Т.11, № 3. С.5–13.
3. Пульмонология. Национальное руководство. Краткое издание / под ред. А.Г.Чучалина. М.: ГЭОТАР- Медиа, 2014. 800 с.
4. Agusti A., Calverley P.M., Celli B., Coxson H.O., Edwards L.D., Lomas D.A., MacNee W., Miller B.E., Ren- nard S., Silverman E.K., Tal-Singer R., Wouters E., Yates J.C., Vestbo J., Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators. Characterization of COPD heterogeneity in the ECLIPSE cohort // *Respir. Res.* 2010. Vol.11, №1. P.122. doi: 10.1186/1465-9921-11-122
5. Almagro P., López García F., Cabrera F.J., Montero L., Morchón D., Díez J., Soriano J.B., Grupo Epos De La Sociedad Española De Medicina Interna. Comorbidity and gender-related differences in patients hospitalized for COPD. The ECCO study // *Respir. Med.* 2010. Vol.104, №2. P. 253–259. doi: 10.1016/j.rmed.2009.09.019
6. American Lung Association. Trends in COPD (chronic bronchitis and emphysema): morbidity and mor- tality. Washington, DC: American Lung Association. 2013. URL: <http://www.lung.org/assets/documents/research/ copd-trend-report.pdf>.
7. Ancochea J., Miravittles M., García-Río F., Muñoz L., Sánchez G., Sobradillo V., Duran- Tauleria E., Soriano J.B. Underdiagnosis of chronic obstructive pulmonary dis- ease in women: quantification of the problem, determinants and proposed actions // *Arch. Bronconeumol.* 2013. Vol.49, №6. P.223–229. doi: 10.1016/j.arbres.2012.11.010
8. Aryal S., Diaz-Guzman E., Mannino D.M. COPD and gender differences: an update // *Transl. Res.* 2013. Vol.162, №4. P.208–218. doi: 10.1016/j.trsl.2013.04.003
9. Aryal S., Diaz-Guzman E., Mannino D.M. In- fluence of sex on chronic obstructive pulmonary disease risk and treatment outcomes // *Int. J. Chron. Obstruct. Pul- mon. Dis.* 2014. Vol.9. P.1145–1154. doi: 10.2147/COPD.S54476
10. Assaggaf H., Felty Q. Gender, estrogen, and oblit- erative lesions in the lung // *Int. J. Endocrinol.* 2017. Vol.2017. P.8475701. doi: 10.1155/2017/8475701.
11. Balgoma D., Yang M., Sjödin M., Snowden S., Kar- imi R., Levänen B., Merikallio H., Kaarteenaho R., Palm- berg L., Larsson K., Erle D.J., Dahlén S.E., Dahlén B., Sköld C.M., Wheelock Å.M., Wheelock C.E. Linoleic acid-derived lipid mediators increase in a female-dom- inated subphenotype of COPD // *Eur. Respir. J.* 2016. Vol.47, №6. P.1645–1656. doi: 10.1183/13993003.01080- 2015
12. Becklake M., Kauffmann F. Gender differences in airway behaviour over a human life span // *Thorax.* 1999. Vol.54, №12. P.1119–1138.