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# Tuberculosis in women of reproductive age

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**Abstract**
The literature review presents data on the problem of respiratory tuberculosis in women of reproductive age. The review focuses on the epidemiology of tuberculosis in young women, their medical and social characteristics, factors predisposing to the disease, clinical peculiarities and drug resistance of the pathogen.

**Keywords**: tuberculosis, women's health, pregnancy.
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# Туберкулез у женщин репродуктивного возраста

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**Резюме**
В обзоре литературы представлены данные по проблеме туберкулеза органов дыхания у женщин репродуктивного возраста. Рассмотрены вопросы по эпидемиологии туберкулеза у молодых женщин, их медико-социальная характеристика, факторы, предрасполагающие к развитию заболевания, клинические особенности и лекарственная устойчивость возбудителя.

**Ключевые слова:** туберкулез, женское здоровье, беременность.
**Конфликт интересов.** Автор заявляет об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.
**Источники финансирования.** Исследование проведено без спонсорской поддержки.
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## Introduction

Tuberculosis (TB) morbidity has declined steadily over the last years in the Republic of Belarus. However, Belarus is still among the high-priority countries for TB in the European region and bears the highest burden of multi-drug resistant (MDR) TB [1]. The World Health Organization (WHO) admits that men globally are more likely to develop TB, but at the same time, TB in women produces a hidden social-economic burden not to be reflected with epidemiological indices [2, 3]. TB affects women at an age of their highest reproductive, social, and economic activity, which makes the most negative impact on families, states, and health care systems [2, 3]. TB is one of the five most frequent infectious death causes in young women and mothers [2, 3, 4, 5, 6, 7]. The problem is even more serious in high HIV associated TB prevalence regions [3, 4, 5, 6, 7]. TB in women is also epidemiologically important due to close contacts with children, which promotes the transmission of the TB infection [2, 3, 8].

Thus, a comprehensive study of TB in young women is topical for the Republic of Belarus and Gomel region in particular, as it is the one with the highest TB and HIV/TB prevalence. The greatest attention is to be paid to the epidemiology of TB in young women, its social-economic significance, factors predisposing to TB and clinical characteristics of the disease in women.

## Epidemiology of TB in women of reproductive age

There is no global complete open access epidemiological information on TB in women

of reproductive age. Available evidence reflects only the situation in some regions of the world and has not been updated for many years. Thus, the latest world data on women's TB morbidity and mortality given in a WHO survey cover those from 1990 to 2013. More than 3 million TB cases and more than 500 thousand TB deaths in women are registered annually [4]. 900 million women worldwide have latent TB infection, which may progress to active disease [7]. The rates of TB morbidity, mortality and global TB burden are unknown for women of reproductive age and particularly pregnant women [6].

The research studying the sex and age structure of TB cases in the regions neighboring the Republic of Belarus showed an age-related peak incidence rate in women 25–34 years of age [9, 10]. Some regional investigations showed increasing TB mortality in young women during the first decade of the XXI century, particularly among those with the HIV-positive status [9].

The proportion of women's TB in the Republic of Belarus is about 25 % of new cases [1]. Few publications focusing on the sex / age structure of TB in Belarus have showed that women get sick with TB most often at the age of 25–44. The men to women ratio among patients with newly diagnosed TB is 3:1, and women of reproductive age have drug resistant TB more often than elder ones [11].

Globally obstetrical conditions are most often to cause unfavorable pregnancy course and maternal mortality. Infectious diseases cause about 28 % of the situations and TB is among the most frequent ones [2, 3]. There are no open access epidemiological data on the TB morbidity and prevalence in pregnant women as well as on HIV-associated and drug resistant TB. Therefore, many publications admit the necessity of a comprehensive epidemiological evaluation of TB in this category of patients [6, 7, 9, 11, 12, 13].

## Medical and social aspects of TB in young women

Social related characteristics of men and women refer to "gender" unlike biological sex determinants. Higher TB rates in men may partly reflect epidemiological differences in their contacts with TB transmitters, risk of getting infected and progressing to disease. Some researches point out that women at early reproductive age may have a higher risk of infection to disease progression and higher mortality than men [2, 12].

TB in young women relates to both medical and socio-economic category. The health of young women greatly determines the demographic perspectives of a state and general well-being of families which closely associates with the most maternal role to give birth and raise children, as well as women's social and economic activities [2, 12]. Another important point is that mothers may transmit TB to their children having the closest contact with them [2, 3, 8].

Only a few Russian publications give social characteristics of women with TB. Researches carried out in the neighboring regions are obviously the most important for the Republic of Belarus due to similar epidemiological and socio-economic characteristics. The health care systems are also analogous and have traditionally prevailing specialized anti-TB services. Studies performed in Belarus and Russia have showed TB to equally affect women living in urban and rural areas [9, 10, 11]. Higher TB prevalence and less effectively organized TB screening were found out among unemployed women [11]. The women with TB found by XR screening were shown to be often MTB positive [11], which refers to longer lasting respiratory symptoms. The situation leads to accumulation of TB infection and its transmission to children who are the most susceptible. The unfavorable social status related to unemployment and homelessness was found to increase the risk of active TB development [9, 10, 11].

In the Republic of Belarus, the only research studying the social aspect of TB in women of reproductive age has been carried out in the Grodno region. Its findings presented in 2020 showed that 60 % of women firstly diagnosed with TB are unemployed despite their working age. Alcohol addicts were shown to make a higher proportion among women with drug-resistant TB than those with drug-sensitive TB (42.1 % compared to 25.7 %). Permanent disablement occurred in 13.1 % of female patients with drug-resistant TB and in 25.8 % of those with drug-sensitive TB [11]. These data must be obligatory considered when developing anti-TB measures for women in the Republic of Belarus.

## Factors contributing to TB development in women of reproductive age

The risk factors of active TB development have been studied for many decades and are quite well-known. These are HIV-infection, immunosuppression, and cachexia of any genesis,

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diabetes mellitus and others [3, 4]. The WHO underlines the importance of social factors for the TB development while admitting women to have a lower social risk than men [3]. Generally, women, if covered by available medical care, have better a health status as they pay more attention to it. This might be explained by pregnancy planning, taking more responsibility to medical recommendations and routing medical screenings [14, 15]. Thus, greater susceptibility to TB among women of reproductive age might have biological determinants. Therefore, to reveal and study the determinants is a priority task [3, 15, 16, 17, 20, 21].

The genetic determinants of susceptibility to TB have been recently reported to exist including those associated with the X-chromosome, which concerns gender differences in the development of the anti-tuberculous immune response. However, the lacking data about gene polymorphism cannot be used in clinical practice yet [20].

Immunity / hormonal interactions, as well as the influence of the sex hormones on the defense mechanisms and anti-TB response are being currently studied [17, 19, 20, 22, 23, 24]. Obviously, an understanding of TB activation triggers and infection to disease development in women must be related to this. The clue is likely to be found in these studies. The role of the sex hormones is also strongly confirmed by the fact of absent sex differences in TB susceptibility in boys and girls before puberty [20].

The male and female hormones have a different influence on the functions of T-lymphocytes, neutrophils, macrophages, dendrite cells. Almost all components of the immune response are stimulated by the male and female sex hormones. Thus, it can be significant for anti-TB protection [20, 25, 26]. Adequate Th1 immune response is vital to resist mycobacterium tuberculosis (MTB). Estrogens are considered to promote a Th1-response. However, scientific studies show that the immuno-hormonal influence on the balance of a Th1/Th2 immune response is quite complicated. Thus, low levels of 17-estradiole potentiate a Th1-response leading to increased levels of tumor necrosis factor alpha (TNF-α). The high level, correspondingly, shifts the balance to Th2-reaction with a decrease in the cytokine level. The sex hormones also stimulate the functions of T-regulator lymphocytes. On the one hand, it might prevent effective MTB elimination. On the other hand, it might limit tissue alteration [25].

Estrogens promote the production of TNF-α and ɣ-interferon and involve vitamin D into immune response [25, 27]. However, its role in anti-TB immunity remains undefined [25].

Macrophages are the main effector cells of anti-tuberculous immunity. The potentiating effect of estrogens on macrophages is considered certain. However, the real effect of the sex hormones on Th1/Th2 balance is much more complicated. Cell necrosis is known to contribute to MTB multiplication, whereas apoptosis — the regulated process — limits bacteria reproduction and stimulates defence. The necrosis / apoptosis balance is regulated by the humoral immune factors, which are in turn influenced by estrogens and progesterone [19, 23, 25].

Progesterone is a potent regulator of immune responses. It is also known as a natural suppressor and modulator of T-dependent immune reactions. Its influence on the functionality of T-lymphocytes, phagocytic activity of neutrophils and macrophages has also been described [19, 20, 23, 25, 28, 29]. Immune response effectors are directed by progesterone Th2-way stimulation and suppression of NK-cells. Progesterone is a key molecule involved in the regulation of Th1/Th2-cells, which is necessary for successful pregnancy. Progesterone has the leading role in the modulation of T-reg-cells. It advances the reversible suppression of cytotoxic cells proliferation and decreases the levels of TNF-α and ɣ-interferon, which are the most important Th1 cytokines [25, 27, 28, 29].

Spontaneous apoptosis of neutrophils is stronger limited by both estrogens and progesterone in women compared to men. Neutrophils cause a paraspecific tissue reaction and increase alteration through T-suppressors inhibiting lymphocytes [30]. The role of neutrophils in the maintenance of effective anti-TB defense remains unclear [20, 25, 31].

In different periods of life, woman's organism endures global hormonal modifications such as during pregnancy and labor, within the postpartum period, after abortion (spontaneous or medical), on taking oral contraceptives. The conformations affect the immune status. The mechanisms of these immuno-hormonal interactions and their predicting effects require thorough studies to be used in the diagnostic algorithm for TB in women [25, 32, 33].

The investigation of the hormonal profile in women with pulmonary TB has showed an abnormal interrelation between the pituitary gonadotropes, suprarenal and sex gland hormones. It has found impaired ratios of follicle-stimulating hormone and luteinizing hormone, increased levels of cortisol, estradiole,

progesterone and prolactine, decreased levels of testosterone [32]. These abnormalities may determine TB development as well as be determined by TB. The detection of these disorders is important both for the diagnosis and prevention of TB in women [18, 19, 20, 22, 32].

The sex hormones influence the extension of TB lesions, MTB concentrations in affected tissues, severity and progression of TB inflammation at early and advanced stages [20, 22]. Thus, the experimental study has showed that the female sex hormones accelerate the severity of inflammation in lung tissues, cause early formation of granulomas and significantly elevate the levels of such humoral immune factors as TNF-α, ɣ-interferon, interleukin-12 in blood serum [22]. Testosterone was found to be the hormone which enhances TB susceptibility [22].

The particular interest makes the question whether immune-hormonal interactions alter results of blood tests to detect anti-TB immune response — ɣ-interferon release assays. Laboratory tests are preferable for pregnant women [35, 36, 37]. However, the informative value and specificity of ɣ-interferon release assays in pregnant women have not been yet completely studied.

All the mechanisms might be important during pregnancy while the problem needs a special discussion.

## Clinical manifestations of TB in women of reproductive age

The study of TB lung manifestations in young women is necessary to substantiate the algorithms of early diagnosis of the disease in target groups of patients.

Microbiological confirmation is a necessary standard of TB diagnosis nowadays [37, 38]. Quite often young women do not produce high concentrations of MTB in the sputum, therefore it appears impossible to find the pathogen in their samples especially by acid fast microscopy, which is a test with lacking sensitivity for early TB stages [10, 39, 40]. Firstly, that impedes the diagnosis, secondly, microscopy does not identify acid fast species and does not differentiate drug sensitive or resistant MTB which is critical in a high prevalence rate of MDR-TB. Moreover, undetectable concentrations of MTB in the sputum do not exclude MTB transmission especially to the most susceptible percipients. Children have the greatest risk of MTB transmission in a case of mother's TB disease due to the closest and prolonged contact [8]. Summarizing the substantiations, highly sensitive molecular genetic methods are the most valuable for TB diagnosis in young women, as PCR tests are also much faster than culture cultivation [34, 35, 36]. Immunological lab tests for MTB detection, which are as highly sensitive as specific, must also be used for sputum negative TB suspects in complex diagnostics. A thorough analysis of MTB positive cases and those with undetectable concentrations of MTB in the sputum among women of reproductive age means to develop the optimal diagnostic approach using the whole arsenal of microbiological, genetic molecular, immunological and radiological options.

As for the clinical variability of lung TB, focal and infiltrative forms prevail in young women [10, 11, 15, 32]. Disseminated forms occur most rarely. However, young women, including those with a HIV-negative status with no evident risks, may also develop extended pulmonary lesions. Actually, such cases are difficult to recognize due to unawareness and absence of concern for potentially severe and disseminated TB disease in women of reproductive age. Moreover, the disease might be not associated with high concentrations of MTB in the sputum for a long time, which impedes the pathogen detection. The clue to proper diagnosis should be a clear understanding of diverse TB symptoms and thorough investigation of the disease history, the duration and severity of intoxication and respiratory symptoms. Highly sensitive PCR and immunological tests are to be used. Microbiological and molecular genetic testing of biopsy material for MTB, together with histology, is obligatory and critically important [39].

The clinical peculiarities of TB in women with different risk factors are to be further investigated. HIV-associated TB often has a manifest presentation and pneumonia-like course. The destruction of lung tissue and high concentrations of MTB in the sputum are often found in both immune compromised patients and alcohol abusers [10, 11, 15]. Thus, differentiated algorithms for the contingents are needed. The diagnostic approach should focus on the clinical nuances of TB in young women and form wariness in medical practitioners and specialists.

Primary and secondary MTB drug-resistance in women requires a particular attention. An understanding of their significance as a source of TB infection is necessary for an objective estimation of the women's role in the transmission of multi-resistant MTB among population. The estimation of MDR-TB prevalence among young women is important for the

optimization of TB diagnosis in women as well in pregnancy. Invasive diagnostics, such as fibrobronchoscopy, video-assisted thoracoscopy with lung biopsy are limitedly used during pregnancy. It is very important to be aware about possible primary MTB drug resistance in young women to clearly substantiate the endoscopic manipulations for obtaining bronchial aspirate or biopsy material for MTB detection and drug susceptibility testing. Today there is no available comprehensive information about MDR-TB morbidity and prevalence among young women.

## Conclusion

It is very important to develop a comprehensive substantiated approach to TB diagnosis in women of reproductive age including pregnant ones. It must be based on thorough consideration of early manifestations, purposeful search of symptoms and application of MTB detecting tests for patients with respiratory or intoxication complaints during pregnancy. It is necessary for saving mothers` health and prevention of MTB transmission to newborns and to other pregnant and postpartum women in inpatient and outpatient medical centres.

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