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Genital tuberculosis as a socially significant disease

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ABSTRACT

Globally, tuberculosis (TB) is the second leading cause of death from infectious diseases after COVID-19. TB of the female genital organs is a type of extrapulmonary TB. Clinically pronounced and latent forms of TB can cause both primary and secondary infertility because of pathogenetic damage to the structure of the fallopian tubes and changes in the susceptibility of the uterine endometrium. Although the true prevalence of genital TB is unknown, it is still a very relevant problem in Russia. This assumption is based on the projected growth of indicators of extrapulmonary TB, an obvious discrepancy between the real incidence and the official figures, and increasing incidence of tubal–peritoneal infertility, which is often caused by genital TB. The diagnosis of TB of the female genital organs is challenging because it does not have specific (so-called “marker”) manifestations. Low diagnostics rates of extrapulmonary TB create a false sense of well-being, which does not reflect its true epidemiological picture. Thus, at present, an optimal diagnostic complex, which would hasten the diagnosis of genital TB in women and consequently prevent the occurrence of associated irreversible changes in the female reproductive system, must be developed. Scientific databases CyberLeninka, ELibrary, and PubMed were searched for relevant articles using the following keywords: “tuberculosis”, “genital tuberculosis”, “infertility and tuberculosis”. Articles published over the past 10 years were analyzed.

Keywords: tuberculosis; genital tuberculosis; literature review; infertility.

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Генитальный туберкулёз как социально значимое заболевание

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АННОТАЦИЯ

Туберкулёз — вторая в мире по значимости причина смерти от инфекционных болезней после COVID-19. Туберкулёз женских половых органов — один из видов внелёгочного туберкулёза. Известно, что как клинически выраженная, так и латентная форма этого заболевания могут быть причинами и первичного, и вторичного бесплодия вследствие патогенетически обусловленного нарушения структуры маточных труб и изменения восприимчивости эндометрия матки. Можно предполагать, что проблема генитального туберкулёза в России сейчас остаётся весьма актуальной, хотя истинная его распространённость неизвестна. Это предположение основывается на фактах прогнозируемого роста показателей заболеваемости внелёгочным туберкулёзом, очевидном несоответствии реальной заболеваемости официальным показателям, а также возрастающей частоте встречаемости трубно-перитонеального бесплодия, причиной которого зачастую становится генитальный туберкулёз.

Известно, что туберкулёз женских половых органов — труднодиагностируемое заболевание. Это определяется в частности тем, что он не имеет специфических (так называемых маркерных) проявлений. Низкие показатели диагностики внелёгочных форм туберкулёза создают ложное ощущение благополучия, не отражая его истинной эпидемиологической картины. Очевидной необходимостью в настоящее время является разработка оптимального диагностического комплекса, применение которого способствовало бы ускорению диагностики генитального туберкулёза у женщин и, как следствие, — предотвращению возникновения обусловленных им необратимых изменений женской репродуктивной системы.

Авторы использовали научные базы КиберЛенинка, eLibrary и PubMed. Статьи искали по следующим ключевым словам: «туберкулёз», «генитальный туберкулёз», «бесплодие и туберкулёз». В работе проанализированы статьи, выпущенные за последние 10 лет.

Ключевые слова: туберкулёз; генитальный туберкулёз; обзор литературы; бесплодие.

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生殖器结核是一种具有社会意义的疾病

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摘要

结核病是仅次于COVID-19的世界第二大传染病致死原因。女性生殖器结核是肺外结核的一种。众所周知，这种疾病的临床表现和潜伏形似可成为原发性和继发性不孕症的原因，这是因为病原体导致了输卵管结构的破坏和子宫内膜易感性的改变。可以认为，俄罗斯的生殖器结核问题仍然非常严峻，尽管其实际发病率尚不清楚。这一假设的依据是，预计肺外结核病发病率将增长，实际发病率与官方数字之间的明显不符，以及输卵管-腹膜不孕症发病率的增加，而这通常是由生殖器结核引起的。

众所周知，女性生殖器结核是一种难以诊断的疾病。这主要是由于它没有特异性（所谓的标记性）表现。肺外结核病的诊断率低造成了一种虚假的幸福感，不能反映其真实的流行病学情况。显然有必要制定一套最佳的综合诊断方法。使用这种综合方法将有助于加快对妇女生殖器结核病的诊断，并防止其对女性生殖系统造成不可逆转的变化。

作者使用了科学数据库CyberLeninka, eLibrary和PubMed。文章使用以下关键词进行搜索：туберкулёз（结核病），генитальный туберкулёз（生殖器结核），бесплодие и туберкулёз（不孕症与结核病）。对过去 10 年发表的文章进行了分析。

关键词：结核病；生殖器结核；文献综述；不孕症。

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BACKGROUND

Tuberculosis remains a global public health concern, ranking second to the novel coronavirus disease (COVID-19) as the leading cause of infectious disease mortality [1]. Approximately one-third of the global population is infected with *Mycobacterium tuberculosis* [1–2]. Additionally, several studies have observed that the prevalence of various menstrual disorders can reach up to 70% in women with tuberculosis [3–4].

Diagnosing genital tuberculosis is challenging, particularly in its early stages. Fertility restoration after treatment is possible in only a small proportion of patients. Previous studies demonstrated a high incidence of infertility (90–97%) in patients with genital tuberculosis. Russian authors have reported that 25–36% of patients were diagnosed with genital tuberculosis 10–15 years after its onset. In many cases, the diagnosis was made incidentally during surgical procedures (10–25%), which has a negative impact on reproductive function [3, 5–7].

EPIDEMIOLOGY

The prevalence of tuberculosis exhibits considerable heterogeneity across Russia, with a prevalence of 31.2 per 100,000 populations in 2021, ranging from 19.8 to 526.9 per 100,000 population observed in various regions. This variation is attributed to differences in diagnostic capabilities, availability of qualified personnel, and the socioeconomic situation in the region. The difficulty of diagnosis results in a low prevalence of female genital tuberculosis, with only 10–15% of women diagnosed with the condition [8]. Low diagnosis rates of extrapulmonary tuberculosis result in a false sense of well-being without reflecting the true epidemiological picture.

The epidemiological situation in the Siberian and Far Eastern Federal Districts is characterized by a high prevalence of tuberculosis, with various localizations accounting for majority of cases [9]. In 2022, 1089 cases of first time active tuberculosis were reported in the Rostov region. Of particular concern was the high prevalence of tuberculosis among people of fertile age, reaching 28.3 per 100,000 population. Genital tuberculosis is the most common extrapulmonary tuberculosis in countries with a high incidence rate, where the proportion of urogenital tuberculosis cases ranges from 33.7% to 45.5%. In contrast, in countries where tuberculosis is not a significant public health concern, urogenital tuberculosis represents a minor proportion of the disease burden. In Russia, urogenital tuberculosis has recently been overtaken by bone and joint tuberculosis [1, 10–12].

Generally, the main causative agent of tuberculosis is considered to be *Mycobacterium tuberculosis*, also called Koch's bacillus (80–95% of cases). However, in rare cases, tuberculosis can be caused by *Mycobacterium bovis*. In

genital tuberculosis, Koch's bacillus is frequently associated with high-risk women, including those infected with HIV; patients undergoing immunosuppressive and radiotherapy treatments; women with chronic stress, inflammatory urogenital tract diseases, menstrual disorders such as oligomenorrhea and amenorrhea, and hormonal disorders; and those belonging to low socioeconomic groups [8].

The following are considered the principal routes of transmission of tuberculosis:

- Airborne (realized when sputum droplets containing enter the alveoli of the lungs) [13–14]
- Air-dust (inhalation of dust particles associated with mycobacteria) [14]
- Alimentary (consumption of food contaminated with mycobacteria, with milk and dairy products from diseased cows and goats being particularly important in human infection) [13–15].

Most authors reject sexual transmission as a transmission route of tuberculosis owing to the vaginal mucosa's resistance to the tuberculosis pathogen [13].

DIAGNOSTICS

Notably, in Russia, tuberculosis is diagnosed specifically by phthisiatricians; however it should obviously be implemented by a physician of any specialty [13].

The methods currently used to diagnose female genital tuberculosis include the following:

1) *Gynecological examination* involves evaluating the condition of the mucous membrane of the vagina and vaginal part of the cervix, the presence of hyperemia, pseudoerosion, milky rashes, and scarring changes in the area of the external pharynx [10–11].

2) *Ultrasound of the pelvic organs* may reveal general, nonspecific signs of inflammation, including the presence of a hydrosalpinx, an increased ovarian size, blurred ovarian contours, a small cystic structure of the ovaries, lateral displacement of the uterus, and fluid accumulation in the Douglas space [13–14]. Conversely, ultrasound of the pelvic organs can reveal signs indicative of tuberculosis. These include an echogenic, heterogeneous structure, which may be encapsulated or caseous, and calcifications in the uterus, its appendages, and the parametrial fascia. Additionally, ultrasound of the ovaries, uterus, and lymph nodes along the iliac vessels may show changes consistent with scarring and adhesions, which result from the tuberculosis process. The sensitivity and specificity of this diagnostic method is 64.4% and 94.7%, respectively. Furthermore, the severity of ultrasound signs of inflammation in response to the tuberculin provocation test enables estimating the degree of tuberculosis process activity [13–14].

3) *Hysterosalpingography* remains a valuable diagnostic tool, although it is limited by its ability to detect subtle anatomical changes that occur during the development of genital tuberculosis. These include the partial or complete

obliteration of the uterine cavity and clear-cut appearance of diverticula and obliteration of fallopian tubes. Obliteration of fallopian tube cavities (distal parts of the tubes may appear as clubs or smoking tubes) and contrast shadows and calcifications in the pelvic region and projections of inguinal lymph nodes may be observed [13–14].

4) *Laparoscopic examination* potentially reveals specific signs of genital tuberculosis, including pelvic adhesions, tuberculous tubercles on the visceral peritoneum of the uterus and fallopian tubes, and foci of caseous necrosis along with inflammatory changes in the uterine appendages [13–14]. An advantage of this diagnostic approach is the ability to collect the required material for further bacteriological and histological studies directly within the procedure itself. In cases wherein surgical correction is required, it can be performed simultaneously (e.g., separation of adhesions, restoration of uterine tube patency) [13].

5) *Morphological examination* enables the detection of specific signs of tuberculous lesions, including perivascular infiltrates and typical tuberculous granulomas, in tissues obtained during separate diagnostic scraping (it is preferable to perform this procedure 2–3 days before menstruation). Cytological examination of uterine cavity aspirate and cervical smears may reveal Pirogov–Langhans giant cells, which are specific for tuberculosis [13].

6) *Laboratory diagnostic methods*: although bacterioscopic examination of pathological material (using a light microscope and Ziehl–Neelsen staining and luminescent microscope and fluorochrome staining) is the most convenient method for diagnosing pulmonary tuberculosis. It is uninformative in cases of extrapulmonary tuberculosis [13–15]. *Culture (bacteriological) testing, also called culture*, is regarded as the gold standard for the detection of *Mycobacterium tuberculosis* [13]. In Russia, diagnosis of all types of tuberculosis, as well as the monitoring of treatment efficacy, is confirmed using microbiological methods. The objects of study include genital tract discharge, menstrual blood, endometrial scrapings, uterine cavity flushes, and the contents of inflammatory foci, among others. However, this diagnostic method requires a considerable length of time to complete (e.g., the growth of the initial mycobacterial colonies is not identified until approximately 1 month after culture), although expensive methods using liquid nutrient media and automated systems are currently being used to shorten the period of cultivation of *Mycobacterium tuberculosis* and facilitate the detection of drug resistance. The irregularity of the use of bacteriological methods in the diagnosis of genital tuberculosis is that *Mycobacterium tuberculosis* is rarely detected by specific tests and samples. The sensitivity of *Mycobacterium tuberculosis* culture does not exceed 3–5% [12]. Furthermore, genital tuberculosis is generally characterized by oligobacillarity.

Among the modern *serological methods* of tuberculosis diagnostics in Russia, enzyme-linked *immunosorbent* assays and *radioimmune* assays are the most prevalent.

These methods are relatively not complicated to use and permit the simultaneous testing of several samples, thereby facilitating screening. *Polymerase chain reaction (PCR)* is a fundamental methodology employed in molecular genetic research and enables the identification of *Mycobacterium tuberculosis* DNA in any available pathological material within 3–4 days. Its key advantages include high specificity (99.8%) and sensitivity (>85%) in laboratory tests and the capacity to verify diagnoses in L-forms. Nevertheless, the observed specificity and sensitivity in clinical practice have been found to be significantly lower than those in laboratory tests [13–15].

Tuberculin tests are a series of diagnostic procedures used to determine the sensitization of the body to *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. The procedure involves the intradermal injection of tuberculin, which is also known as the Mantoux reaction. The results of this reaction can be used to determine whether an individual is infected with *Mycobacterium tuberculosis*; however, it is impossible to determine whether the individual has the disease using this reaction [11, 13–15].

In a large study conducted in 2015 in Cheboksary, Samoylova et al. [16] showed interesting results on the prevalence of genital tuberculosis in patients for in vitro fertilization: 16 of 469 (3.2%) patients were diagnosed with genital tuberculosis for the first time, positive results of *Mycobacterium tuberculosis* detection were obtained in endometrial biopsy specimens, and *Mycobacterium tuberculosis* was not detected in other samples of surgical material and menstrual blood. Histological examination of endometrial biopsy material revealed the presence of nonspecific inflammation, and specific endometrial changes characteristic of tuberculosis were not detected in any endometrial sample or surgical material. Among the women in the main group with newly diagnosed genital tuberculosis, 10 (62.6%) had a positive Mantoux test [16].

CLINICAL SIGNS

Most authors have not observed symptoms specific to genital tuberculosis. However, clinicians have noted impaired patency of the fallopian tubes, chronic lower abdominal pain, and infertility. Menstrual disturbances are probably associated with ovarian parenchyma and endometrium, causing menstrual dysfunction. Oligomenorrhea, amenorrhea, irregular menstruation, algodismenorrhea and, less frequently, abnormal uterine bleeding develop. Depending on the activity of the process, intoxication symptoms, including increased body temperature, rapid fatigue, general weakness, weight loss, and night sweats, may occur [9].

A high incidence of sexually transmitted infections (81.6%) was found in women at risk for genital tuberculosis with reproductive disorders, regardless of the presence of genital tuberculosis. Women with genital tuberculosis are characterized by the presence of a concurrent infection [7].

In the literature reviewed, women with latent genital tuberculosis were found to have lower levels of anti-Müllerian hormone (AMH), poorer reproductive prognosis, and lower efficacy in assisted reproduction therapy (ART) [17].

In Russia, the Omsk region is considered one of the “leaders” in the incidence of genital tuberculosis: this is largely due to its low standard of living, high proportion of young people with preserved reproductive function, and close contact with children. Kravchenko et al. studied 200 female patients with active pulmonary tuberculosis aged 18–40 years who were treated in state hospitals of the Ministry of Health of the Omsk region between September 2013 and February 2014.

For instance, patients with pulmonary tuberculosis mentioned infectious diseases such as hepatitis B, hepatitis C, and HIV infection. In the present study, several cases in patients with pulmonary tuberculosis were observed, including one patient with fibrotic cavernous pulmonary tuberculosis who had had pulmonary tuberculosis for 8 years and experienced six miscarriages. Two other patients with chronic pulmonary tuberculosis (disease duration: 7–10 years) had 10 pregnancies each, which ended in spontaneous abortions before 15–16 weeks of gestation. Furthermore, 30% of patients did not consider it crucial to inform their sexual partners about their disease [18].

Presently, tuberculosis persists as a significant social issue in developed countries. Its global prevalence is estimated to be between 5% and 10%, with an annual increase in new cases in India ranging from 4% to 7%. Consequently, genital tuberculosis and its potential complications are being actively investigated in India. A study by Fowler et al. [19] made reference to the study of Sharma et al. [20], in which 28 women underwent hysteroscopy with or without laparoscopy for suspected Asherman syndrome. Of these women, 67.8% had a history of tuberculosis, and all presented with primary (67.8%) or secondary (32%) infertility. Furthermore, Fowler et al. cited data from Mondal et al. [21] who examined 56 patients with confirmed genital tuberculosis. The average age of the women was 25.6 years. Following treatment, nine patients became pregnant. However, eight of them experienced spontaneous abortions, and only one achieved a successful pregnancy. Unfortunately, most women with genital tuberculosis suffer from infertility and poor fertility prognosis despite ART [19].

In 2023, in India, Sharma et al. conducted a large study describing 374 cases of diagnostic laparoscopy performed in patients with infertility and tuberculosis. The study found that 81% of cases were primary infertility and 18.2% were secondary infertility. Furthermore, the study showed that 83.95% of cases had a positive PCR for *Mycobacterium tuberculosis*. The study identified 164 cases (43.9%) with definitive signs of female genital tuberculosis (FGT). The results indicate that laparoscopy is a valuable diagnostic tool for FGT, with a higher incidence of cases. A further Indian study evaluated ovarian reserve by measuring AMH and antral follicle count (AFC) in 133 infertile women with genital tuberculosis.

AMH and AFC were assessed and compared with controls in all infertile women. The mean AMH (1.88 ± 1.52 ng/ml) and mean AFC (9.0 ± 5.5) levels were significantly lower ($p < 0.001$) than in the control group, which had an AMH of 3.57 ± 2.93 ng/ml and AFC of 12.5 ± 6.0 . The authors concluded that genital tuberculosis should be excluded in women with long-term infertility and low ovarian reserve. Prompt diagnosis and treatment can prevent further deterioration of ovarian reserve and enhance reproductive outcomes [22].

Indian scientists have recently reported the occurrence of salpingo-intestinal fistula, a rare condition that can cause infertility. Tuberculous salpingitis should be considered as a potential cause of salpingo-intestinal fistula in developing countries where tuberculosis is considered endemic [23–24].

PREGNANCY

The incidence of tuberculosis in pregnant and postpartum women is 2–2.5 times higher than in women of the same age in the general population. During pregnancy, due to physiological immunosuppression, severe destructive forms of pulmonary tuberculosis (infiltrative with decay, cavernous, caseous pneumonia, disseminated) with a progressive course develop. The diagnostic challenge posed by tuberculosis during these periods is due to the initial manifestations of the disease (weakness, malaise, decreased appetite, weight loss) that are frequently associated with toxemia of pregnancy. In the second and third trimesters of pregnancy, insufficient weight gain or even a decrease in body weight is a cause for concern. Tuberculosis is often asymptomatic in the initial phase [25–26]. The clinical manifestations of respiratory tuberculosis in the second and third trimesters of pregnancy may be subtle and unexpressive, manifesting as a satisfactory general condition with significant exudative changes in the lungs. The significance of testing during pregnancy is underscored by the fact that 14–47% of pregnant women who undergo testing for tuberculosis exhibit a positive Mantoux tuberculin skin test result. Moreover, most pregnant women with active tuberculosis are unaware of their disease status [25–27].

A review of the literature by Amirova indicated that the combination of pulmonary tuberculosis and pregnancy is mutually aggravating. The progression of tuberculosis was observed in 31.7% of pregnant women and 63.6% of women in labor [28]. Majority of studies have demonstrated that pregnancy has a negative impact on the course and outcome of tuberculosis, resulting in more severe and higher incidence of complications. Furthermore, pregnancy complications, such as anemia, fetoplacental insufficiency, fetal hypoxia, the threat of termination of pregnancy, preeclampsia, pregnancy-induced edema, increased blood pressure, fetal growth retardation, and chronic fetal hypoxia, have been observed. The most prevalent adverse outcomes in maternal and perinatal health are maternal death, miscarriage, preterm birth, low and very low birth weight,

congenital malformations, and other neonatal pathologies [28–31]. The condition significantly deteriorates following delivery due to the combined effects of additional physical activity, blood loss, immune and hormonal state changes, abrupt diaphragm lowering, and abdominal decompression syndrome. Acute hematogenous dissemination of tuberculosis occurs, accompanied by the aspiration of caseous masses into healthy areas of the lungs, resulting in bronchogenic infiltration [30–32].

CONCLUSIONS

Declining fertility and the preservation of women's reproductive health has long been a significant medical and socioeconomic concern that requires attention at the state level. Thus, an optimal diagnostic framework that would facilitate the early diagnosis of genital tuberculosis in women should be developed to prevent the occurrence of irreversible changes in the female reproductive system.

Most authors agree that it is critical to introduce microbiological and histological methods of examination of biopsy material for *Mycobacterium tuberculosis* into the daily practice of obstetrician-gynecologists when examining infertile couples. Concurrently, the World Health Organization advocates for the replacement of microscopy with molecular rapid diagnostic tests as the initial diagnostic test for all women with newly detected signs and symptoms of tuberculosis and patients undergoing (or previously undergoing) treatment for tuberculosis and for the assessment of possible rifampicin resistance [15, 26]. In contemporary medical practice, women undergoing infertility treatment involving ART should undergo a mandatory examination by a specialist in both pulmonary and gynecological medicine to exclude latent and genital tuberculosis [27].

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The urgency of the problem of tuberculosis is confirmed in the article by Nefyodova et al. published in *Digital Diagnostics* in 2023 [33].

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