Tuberculosis as a reason for male and female sexual dysfunction

Ekaterina Kulchavenya[1]
Victor Khomyakov[2]
[1]Novosibirsk Research TB Institute, Novosibirsk State Medical University, Novosibirsk, Russia
[2]Novosibirsk Medical University, Novosibirsk, Russian Federation

Abstract

Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2016, 10.4 million people were affected by TB with more than 1.3 million deaths. One fifth of all TB related death were suffering of HIV. Eighty percent of male patients with pulmonary TB are young men. The problem of the influence of pulmonary TB on the sexual function in men has been covered in medical literature insufficiently. Mostly articles were devoted to urogenital tuberculosis (UGTB) as well as for female genital tuberculosis (FGTB). The negative impact on the reproductive function by both TB as an infection disease and anti-TB therapy was shown in some articles.

Not only genital TB, but also pulmonary TB disturbs both sexual and reproductive functions in males and females. TB patients have to take not less than 4 anti-TB drugs simultaneously for a long time and anti-TB drugs negatively influence on sexual function too.

Keywords: tuberculosis, male, female, urogenital, genitals, infertility, sexual, reproductive

Summary of findings and recommendations

1. Male and female genital tuberculosis (MGTB and FGTB) are a rare form of tuberculosis (TB), but in countries with epidemic TB a large part of patients is underdiagnosed (Level of Evidence – LoE 2).
2. MGTB is mostly (over 50%) associated with lung and/or renal TB (actual or cured), but isolated forms are also possible. Mostly epididymis and prostate are involved (LoE 1).
3. The main route of infection is via hematogenous spread, but direct extension from infected urine and lymphatic spread are also possible (LoE 1).
4. As transmission by sexual contact is possible, sexual partner should also be examined for genital TB (LoE 2).
5. Both *M. tuberculosis* and infection by nontuberculous mycobacterium may cause infertility (LoE 2).
6. Infertility is one of the most common symptom for MGTB and FGTB; sometimes infertility is the first sign of generalized TB (LoE 2).
7. Not only genital TB influences negatively the female reproductive function, pulmonary TB as well causes menstrual abnormalities in 66% of women (LoE 2), so patients with any localization of TB and any problems with reproductive function should also be examined for genital TB involvement (LoE 2).

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1 Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB), including male and female genital organs.

World Health Organization (WHO) recognized TB as a global problem, TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent. In 2016, there were an estimated 1.3 million TB deaths among human immunodeficiency virus (HIV) negative people (down from 1.7 million in 2000) and an additional 374,000 deaths among HIV-positive people. Given that most deaths from TB are preventable, the death toll from the disease is unacceptably high. An estimated 10.4 million people (90% adults; 65% male; 10% people living with HIV) fell ill with TB in 2016 [1].

Urogenital tuberculosis (UGTB) is the second–third most common extrapulmonary manifestation of tuberculosis (TB) and an isolated involvement of genital organs is reported in 5–30% of the cases [2]. About 77% men who died from all forms of TB, had prostate TB, mostly overlooked alive [3]. Prostate TB is important because:

i. It is a sexually transmitted disease [4], [5], [6], [7], [8], [9], [10];

ii. It leads to infertility;

iii. It results, like any prostatitis, in chronic pelvic pain, that significantly reduces quality of life;

iv. It impairs with sexual function, and that again decreases a quality of life [11].

The good sexual life is an integral part of full and happy life of modern human, but some diseases disrupt it. So, 42–67.3% of patients with diabetes and high blood pressure have sexual dysfunction [12], [13], [14], [15]. The majority of TB patients are young men and sexual function is very important for them. TB significantly disturbs patients mentally and physically. Chronic infection, long isolation, intake of big quantity of drugs lead to sexual dysfunction including infertility. Female genital tuberculosis (FGTB) is one of the leading reasons for reproductive dysfunction as well. It is also often overlooked and is diagnosed after surgery only [16].

2 Material and methods

A Medline/PubMed research with key words “tuberculosis sexual dysfunction” resulted in nothing – there were none paper dedicated to this problem. A Medline/PubMed research with key words “genital tuberculosis” resulted in a total of 3,418 titles, 414 within the last 10 years (since 2007), and 207 within the last 5 years (since 2012). A Medline/PubMed research with key words “male genital tuberculosis” resulted in a total of 980 titles, 148 within the last 10 years (since 2007), and 59 within the last 5 years (since 2012). A Medline/PubMed research with key words “female genital tuberculosis” resulted in a total of 2,593 titles, 258 within the last 10 years (since 2007), and 131 within the last 5 years (since 2012). So, female genital tuberculosis is more popular topic (see table 1). All article with key words “genital tuberculosis infertility” were included in the link of papers with key words “genital tuberculosis”.

Table 1: Papers on genital tuberculosis, cited in Medline/PubMed

Search results	**with key words “genital tuberculosis”**	**with key words “male genital tuberculosis”**	**with key words “female genital tuberculosis”**	**with key words “male genital tuberculosis infertility”**
total	3,418	980	2,593	69
within 2007–2017	414	148	258	16

Search results	with key words “genital tuberculosis”	with key words “male genital tuberculosis”	with key words “female genital tuberculosis”	with key words “male genital tuberculosis infertility”
within 2012–2017	207	59	131	5

Among 414 articles with key words “genital tuberculosis” of the last 10 years, 163 (39.4%) were case reports, including cases of tuberculous epididymorchitis and prostatitis following intravesical BCG for superficial bladder cancer [17], 82 (19.8%) mentioned genital tuberculosis in the context of other diseases, 60 articles (14.5%) were dedicated to infertility, mostly female, 48 (11.6%) were associated with HIV infection, 37 papers (8.9%) were dedicated to diagnostic of genital TB, 24 articles (5.8%) were dedicated to therapy, including with multi-drug resistant *M. tuberculosis*, describing the experience of single centers. To estimate the influence TB on sexual function worldwide was almost impossible; most studies have been published in Russian.

Among all 69 articles with key words “male genital tuberculosis infertility” 12 were cases descriptions, 10 – review, two – comments and 14 were dedicated to studies on this problem. Others papers were on infertility without TB, on female infertility and on related factors to infertility.

Sixty literature issues dedicated to problem of TB and infertility as whole, connection with both male female infertility and TB as well as negative influence of TB and anti-TB therapy on sexual function were analyzed and structured.

3 Results

3.1 The problem of tuberculosis

According to WHO data, about one-third of the world's population has latent TB, which means people have been infected by *Mycobacterium tuberculosis* (Mtb) but are not (yet) ill with disease and cannot transmit the disease. People infected with Mtb have a lifetime risk of falling ill with TB of 10%. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who consume tobacco, have a much higher risk of falling ill [1].

TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2016, 10.4 million people fell ill with TB and more than 1.3 million died from TB. This disease is a leading killer of people living with HIV causing one fifth of all deaths [1].

Eighty percent of male patients with pulmonary TB are young men [18], [19], [20], [21], [22]. The problem of the influence of pulmonary TB on the sexual function in men has been covered in medical literature insufficiently and most publications devoted to UGTB as well as for FGTB.

It has been shown that the tuberculous epididymitis is a cause of infertility [23], [24]; the development of excretory-obstructive forms of infertility as a result of male genital TB has also been reported [25], [26], [27]. A number of authors not just only confirmed the role of UGTB in development of infertility in men, but also noted that fertility problems could sometimes be the first sign of male genital TB [28], [29].

3.2 The problem of infertility

Fertility problems are observed in a growing number of couples in many countries[30]. The reported prevalence of subfertility has increased significantly over the past twenty years. It is estimated that for 40% to 50% of couples, subfertility may be a result of female problems, including ovulatory disorders, poor oocyte quality, fallopian tube damage and endometriosis[31]. Male infertility is a common and complex problem affecting 1 in 20 men. Despite voluminous research in this field, in many cases, the underlying causes are unknown. Epigenetic factors play an important role in male infertility and these have been studied extensively[32].

An increasing number of reports suggest that chemical and physical agents in the environment, introduced and spread by human activity may affect male fertility in humans [33]. TB infection as well as anti-TB therapy may be considered like bad environment, and we may expect negative influence of these factors on fertility too.

A retrospective study of 1,512 infertile men showed that compared with non-smokers, smokers had a significant decrease in semen volumes, in the levels of immotile sperms and semen leukocytes. Sperm motion parameters were all lower in the smokers. Further, the percentage of normal morphology sperm was decreased significantly in smokers ($p=0.003$), the sperm morphology was worse with increasing degree of smoking[34].

The damaging effect of oxidative stress is considered to be the underlying cause of subfertility in 30 to 80% of the cases[35]. There are data indicating that prenatal exposure to alcohol may have a persisting adverse effect on Sertoli cells in sons of mothers-alcoholics, and thereby sperm concentration[36].

3.3 Male infertility and tuberculosis

The influence of urogenital infections and inflammation on fertility is still not well known, but 5–12% of men attending infertility clinics had urogenital inflammation in history [23], [37], [38]. Infection has a detrimental effect on sperm quality by reducing of concentration and motility, also urogenital infections may affect the number of morphologically normal spermatozoa. Outcome of urogenital infection often is fibrosis that may cause an obstruction most likely located in the ejaculatory ducts [39], [40].

Chronic prostatitis has been proved to cause scarring of the prostatic and ejaculatory ducts, resulting in low seminal volume with low fructose and alpha-glucosidase [37]. An excisional testicular biopsy was performed in all men presenting with <1 million spermatozoa per milliliter and was found that 50% had a normal spermatogenesis. A history of male accessory genital infection was found in 12% of the men and 10% had abnormalities found on transrectal ultrasound of the prostate (like oedema, dilatation of the seminal vesicles and ejaculatory ducts) intraprostatic calcifications and dilatation of the periprostatic venous plexus. Ejaculatory duct obstruction is a common cause of male infertility and infections are present in at least 22–50% of these men [41].

A case of azoospermia due to UGTB was reported[42]. A 38-year-old man had 4-year sterility. Obstructive azoospermia due to previous male genital TB because of his treatment history, calcifications in the seminal vesicles and nodules in the right epididymis was suspected. After microsurgical epididymal sperm aspiration was performed twice without success, authors extracted sperm from his testis (testicular sperm extraction) and fertilized his wife's oocyte by intracytoplasmic sperm injection.

Late diagnosed TB epididymitis has less chance for recurrence by chemotherapy and may lead to sterility [23]. If antituberculous drugs are always effective in initial stages, surgery is usually radical, and rarely conservative. The latter procedures are vasovasostomy or vasoepididymostomy whose results are very hazardous[28].

Moon et al. [43] investigated the influence of previous tuberculous epididymitis in patients with obstructive azoospermia. Embryo quality and pregnancy outcome in sperm retrieval and

intracytoplasmic sperm injection (ICSI) were comparable in both the tuberculous and the nontuberculous obstructive azoospermia patients. Although there was a preponderance of testicular sperm used in the tuberculous obstructive azoospermia group, authors concluded that previous TB epididymitis in patients with obstructive azoospermia does not affect the outcome of sperm retrieval and ICSI [43].

Not only Mtb may cause a male infertility; infertility from infection by nontuberculous mycobacterium was reported by Indudhara et al. [44]. They presented a case of seminal vesiculitis due to *Mycobacterium gastri* in a diabetic patient leading to male infertility. Improvement in semen quality was noticed after 6 months of therapy with isoniazid, ethambutol and rifampicin.

Fraietta et al. [24] described a case of TB of seminal vesicles as a cause of aspermia. Sonographic findings in tuberculous epididymitis and epididymo-orchitis, such as the heterogeneous and hypoechoic swelling of the epididymis or the concomitant hypoechoic lesion of the testis with associated sinus tract or extratesticular calcifications may explain the nature of infertility in male genital TB patients[45], [46].

Male genital TB especially TB epididymitis provide a high risk of male infertility secondary to vasal or epididymal obstruction or testicular necrosis[28].

Infertility may be a first symptom of male genital TB. Lübbe et al. [29] reported a case of a 26-year-old male complaining about primary infertility revealed leukocytospermia and a normal sperm count. The diagnosis of UGTB was based on positive morning urine culture.

Tzvetkov and Tzvetkova [47] have analyzed history cases of 69 male genital TB patients. TB epididymitis was diagnosed in 78.26%; in 68.12%, unilateral affection was evident and involvement of left and right sites was similar. In 40.58% of patients, various grades of sperm quality alterations were diagnosed. Almost one-third of cases showed co-morbidity and 36.24% association with TB of other organs and systems. Authors concluded that male genital TB has a considerable impact on fertility and still remains a challenging medical problem [47].

Sole-Balcells et al.[27] investigated spermiogram in 50 UGTB patients, all under 40 years old. The patients were divided into two groups: the first one included patients showing clinical alteration of the genital tract, and the second one included patients without any clinical involvement of genitals; they had kidney TB only. All patients with clinical alterations in the genital tract, showed also alterations in the cytomorphological and/or in the biochemical characteristics of ejaculate. 75% of the patients with kidney TB without genital lesions showed oligoasthenozoospermia too. In spite of the treatment established, no improvements were observed in the spermiogram in both groups. Their results were confirmed later [26].

3.4 Female infertility and tuberculosis

TB is one of the commonest causes of infertility in underdeveloped countries. Sheikh [48] reported a woman with primary infertility – she was diagnosed by laparoscopic examination and culture of tubercles and peritoneal fluids. She was found to have extensive genital and intraperitoneal TB. The tubercles were covering the viscera so extensively that identity of intraabdominal organs was impossible.

Genital TB is common in India – and it is common reason for female infertility there [49]. A total of 85 women of genital TB, who underwent diagnostic laparoscopy for infertility or chronic pelvic pain were enrolled in the retrospective study. Authors considered a significant pelvic morbidity, fibrosis and tubal damage as main reason for infertility in FGTB patients [50].

Singh et al. [51] also point out that genital TB is the major causative factor for severe tubal disease requiring assisted reproduction in developing countries like India. Earlier Parikh et al. [52] noted that TB, a chronic infectious disease, is one of the major etiologic factors of female tubal infertility, especially on the Indian subcontinent.

Tripathy and Tripathy [53] estimated the incidence of genital TB in infertility and tubal factor infertility were 3 and 41%, respectively. The incidence of infertility in FGTB was 58%. All patients were symptom

free and no evidence of TB was detected after the end of the chemotherapy. The risk factors not conducive to pregnancy were secondary amenorrhea, no endometrium on curettage, and negative chromopertubation. The conception rate is low, i.e. 19.2%, the live birth rate being still low, i.e. 7.2% [52].

Tubal block is the sequel of FGTB. Among 60 patients, 60% had primary sub-fertility and 40% had secondary sub fertility. Most common tubal pathology was adhesion (36%). There were bilateral tubal blocks in 18 (60%) and unilateral tubal block in 12 (40%) cases [54].

Not only genital TB negatively influences female reproductive function, pulmonary TB as well caused menstrual abnormalities in 66% of women. After completing anti-tuberculosis treatment, 76% of women with menstrual abnormalities resumed normal menstrual cycles [55], [56], [57], [58].

3.5 Negative influence of tuberculosis and anti-TB therapy on fertility

Not only TB disease has negativ impact on sexual / reproductive function, anti-TB therapy also may disturb this function.

The intravaginal latency time before onset of TB was estimated retrospectively and in 3 months on anti-TB therapy in 98 pulmonary TB male patients. Before anti-TB therapy 14.3% of pulmonary TB patients had ejaculatory disorders: 10.2% had premature ejaculation, and 4.1% delayed ejaculation. The remaining 85.7% patients had normal ejaculation.

After three months of the therapy with 4 anti-TB drugs (isoniazid, rifampicin, pyrazinamide and streptomycin) the proportion was changed significantly. The share of patients with normal ejaculation decreased to 61.2%. On contrary, frequency of premature ejaculation increased twice (20.4%), and delayed ejaculation – in 4.5 times (18.4%) [59].

Authors emphasized that proportion of ejaculatory disorders in patients with pulmonary TB before a start of anti-TB therapy was the same as in population as whole. So, TB as a disease doesn't damage ejaculatory function – but anti-TB therapy does it. The high growth of delayed ejaculation as a side effect of anti-TB therapy may be explained by neurotoxicity of anti-TB drugs [59].

Deterioration of all parameters of copulatory act, from sexual desire to orgasm, was found in 105 patients with pulmonary TB aged of 18 to 39 years, in spite of absence of any related diseases of urogenital system [60]. The degree of sexual dysfunction in the group of patients with cavernous pulmonary TB was significantly higher and it correlated with a high degree of severity of intoxication syndrome.

Anti-TB chemotherapy could improve fertility of a man with pulmonary TB by arresting the system inflammatory process and reducing intoxication. But even in 6 months of the treatment their sexual function was nor normal [60].

4 Conclusion

Tuberculosis disrupts sexual function including reproductive one in male and female patients – both genital TB and pulmonary TB. TB patients have to take not less than 4 anti-TB drugs simultaneously for a long time and anti-TB drugs negatively influence on sexual function too. It is necessary to have high index of suspicion for in-time diagnosis of genital TB, because infertility may be a first symptom of this disease. Protective pathogenetic therapy is indicated for TB patients.

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Corresponding author: Prof Ekaterina Kulchavenya, Novosibirsk Research TB Institute, Novosibirsk State Medical University, Novosibirsk, Russia, E-mail: ku_ekaterina@mail.ru

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