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Comprehensive analysis of vaginal microbiota in Chinese women with genital tuberculosis: implications for diagnosis and treatment

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Abstract

Background Tuberculosis remains an infectious disease of global concern, with potential impacts on respiratory and intestinal microbiota owing to prolonged broad-spectrum antibiotic therapy. Despite its potential to cause infertility, the vaginal microbiota of women with genital tuberculosis remains poorly understood. We comprehensively analyzed the vaginal microbiota in Chinese women with genital tuberculosis.

Results We recruited women with pelvic ($n=28$), endometrial ($n=16$), and pulmonary ($n=12$) tuberculosis as the research group, and healthy women ($n=11$) as the control group. Vaginal discharges were collected for metagenomic analysis of its microbiota. The alpha diversity of the vaginal microbiota in women with genital tuberculosis was slightly higher than that in healthy women, though the difference was not statistically significant ($P=0.23$). Similarly, no significant differences in alpha diversity were observed between women with genital and pulmonary tuberculosis ($P=0.82$) or between those with pelvic and endometrial tuberculosis ($P=0.82$). Notably, the lowest alpha diversity was recorded six months to one year after initiating anti-tuberculosis treatment, with this decline being statistically significant ($P=0.023$). The dominance of Lactobacillus iners in the vaginal microbiota was more common in women with genital tuberculosis than that of Lactobacillus crispatus. Furthermore, the abundance of short-chain fatty acid -producing anaerobes, such as Actinomycetes, Streptococcus, and Finegoldia, were significantly increased. Short-chain fatty acid precursor pathways, including the ko03010 ribosome pathway, ko00970 aminoacyl-tRNA synthesis, ko00230 purine metabolism, ko00240 pyrimidine metabolism, and ko00010 glycolysis gluconeogenesis pathway, were significantly upregulated in women with endometrial tuberculosis.

Conclusions Extrapulmonary tuberculosis, particularly genital tuberculosis and its associated vaginal dysbiosis impacts female fecundity. Vaginal dysbiosis is more pronounced when M. tuberculosis invades the endometrium. Given the effect of antibiotics on vaginal flora, probiotic combined interventions could be used as a future research direction.

Clinical trial number Not applicable.

Keywords Genital tuberculosis, Vaginal microbiota, Female infertility, Antibiotic therapy, Short-chain fatty acids

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Background

Tuberculosis (TB) is an infectious disease of global concern and ranks among the top ten causes of death, particularly prevalent in low- and middle-income nations [1]. Mycobacterium tuberculosis infection typically presents as clinically asymptomatic latent tuberculosis, with the bacterium capable of remaining dormant for extended periods before reactivation, leading to chronic lung lesions. Active TB results in morbidity and mortality rates ranging from 5 to 10% [1]. Each year, millions of TB patients receive antibiotic therapy, with treatment courses typically lasting over six months [2]. This prolonged antibiotic regimen significantly impacts the gut and pulmonary microbiota of patients with TB over the long term [3].

In the past decade, projects focusing on the human microbiome and integrated human microbiome [4] have extensively explored region- and disease-specific communities within the human body alongside their potential functions. Emphasis has increasingly focused on understanding the dynamic and bidirectional interactions among microbiota, the host, and the immune system. Various "-omics" approaches have broadened our knowledge of the co-evolution of commensal microbiota with their hosts, playing a central role in shaping health and susceptibility to disease. One illustrative example investigated in tuberculosis (TB) is the interplay between the microbiota of the gut and respiratory tract, termed the gut–lung axis [5]. M. tuberculosis infection is associated with gut "dysbiosis" and typically, the fecal microbiota of patients with newly diagnosed and recurrent TB consistently exhibit reduced microbial diversity compared with that in healthy controls [6, 7]. Similar findings are observed in respiratory microbiota, where a more abundant microbial community is observed in patients without M. tuberculosis infection [8]. Additionally, respiratory inflammation impacts the diversity of gut microbiota. Bacterial components, metabolites, and immune signals traverse between the lungs and intestines via the bloodstream, indicating a bidirectional gut–lung axis [9].

While M. tuberculosis primarily affects the respiratory system, approximately 15% of infections occur at extrapulmonary sites worldwide, leading to additional complications [10]. Female genital TB, a leading cause of female infertility, accounts for approximately 9% of all extrapulmonary TB cases [11–13]. In regions with high TB prevalence, up to 25% of women with infertility may have genital TB [10], with 75% of clinical cases affecting women of reproductive age (20–45 years) [14]. The adverse effects of genital TB on reproductive anatomy and physiology can be severe when left untreated [15]. In 90–100% of cases, fallopian tubes are gradually affected, whereas the uterine endometrium is involved in 50–80% of cases [15]. Infertility affects approximately 40–80% of genital TB cases and may be the sole manifestation in asymptomatic women [16]. The female genital microbiota is closely associated with reproductive health [17], with the proximity of the genital tract to the gut facilitating close communication between their microbiota.

The understanding of the vaginal microbiota in women with genital TB remains limited, and the impact of anti-TB treatment on the vaginal microbiota has yet to be clarified. Therefore, in this study, we recruited Chinese women diagnosed with simple pulmonary, pelvic, and endometrial TB, as well as healthy controls, to conduct a comparative analysis of their vaginal microbiota. Simultaneously, we assessed the influence of anti-TB treatment duration on vaginal microbiota diversity. We believe that our findings would provide insights into protecting the reproductive and microecological health of women with M. tuberculosis infection.

Results

Demographics

We included a total of 28 patients with pelvic TB, 16 with endometrial TB, 12 with pulmonary TB, and 11 as healthy controls. Age matching was observed among the groups ($P = 0.265$; Table 1). Notably, three patients had pelvic TB, and one patient with endometrial TB was diagnosed with infertility. While most patients underwent standard anti-TB therapy, treatment duration varied (Table 1). The number of white blood cells in vaginal secretions was significantly higher in women with TB ($P < 0.001$; Table 1). However, vaginal microecological test results did not significantly differ among the groups ($P = 0.548$; Table 1).

Vaginal microbiota of women with tuberculosis

The alpha diversity of the vaginal microbiota in women with pelvic and endometrial tuberculosis, collectively termed genital tuberculosis (GTB), was marginally higher than that in healthy women; however, this difference was statistically insignificant (Fig. 1A, $P = 0.23$). The alpha diversity of vaginal microbiota did not significantly differ between women with GTB and those with pulmonary TB (Fig. 1B, $P = 0.82$) or between those with endometrial and pelvic TB (Fig. 1C, $P = 0.82$). However, the alpha diversity of vaginal microbiota was significantly lower in women receiving anti-TB treatment for six months to one year compared with those who did not receive any treatment (Fig. 1D, G1&G3, $P = 0.023$). While the vaginal microbiota of women receiving treatment for over a year or discontinuing medication exhibited higher alpha diversity, this was statistically insignificant (Fig. 1D).

Microbiota taxonomy analysis revealed that, whether women with pelvic or endometrial TB, the vagina is dominated by Firmicutes-Lactobacillus(Fig. 2A, B). Further analysis of the subtypes of Lactobacillus found that

Table 1 Demographics of participants

	Normal control (*n* = 11)	Pelvic TB (*n* = 28)	Endometrial TB (*n* = 16)	Pulmonary TB (*n* = 12)	*P*
Age(years old)	33.2 ± 3.6	33.1 ± 8.4	37.6 ± 8.6	32.3 ± 9.5	0.265
Infertility					0.460
No	11(100.0%)	25(89.3%)	15(93.8%)	12(100.0%)	
Yes	0	3(10.7%)	1(6.2%)	0	
Number of vaginal white blood cells					<0.001
0–5/HPF	9(81.8%)	6(21.4%)	1(6.2%)	1(8.3%)	
5–15/HPF	1(9.1%)	17(60.7%)	12(75.0%)	8(66.7%)	
>15/HPF	1(9.1%)	5(17.9%)	3(18.8%)	3(25.0%)	
Vaginal microecology					0.548
Normal	8(72.7%)	23(82.1%)	12(75.0%)	10(83.3%)	
BV	1(9.1%)	0	2(12.5%)	0	
VVC	2(18.2%)	5(17.9%)	2(12.5%)	2(16.7%)	
Duration of anti-TB treatment					0.073
No treatment	-	10(35.7%)	8(50.0%)	2(16.7%)	
Less than half year	-	7(25.0%)	1(6.2%)	7(58.3%)	
Half to one year	-	3(10.7%)	1(6.3%)	1(8.3%)	
Over than one year	-	5(17.9%)	6(37.5%)	2(16.7%)	
End of treatment	-	3(10.7%)	0	0	

Note: HPF, high power field. General statistical analysis conducted using SPSS 19.0 software, with analysis of variance (ANOVA) for age comparison and Chi-square or Fisher exact test for other comparisons. Statistical significance was denoted by $P < 0.05$

the proportion of L. iners in women with pelvic and endometrial TB was higher than that of L. crispatus (Fig. 2C). A small proportion of miscellaneous bacteria are also found colonizing the vagina in women with genital tuberculosis. At the phylum level, Proteobacteria and Tenericutes were more abundant in women with pelvic TB, whereas Actinobacteria was more common in women with endometrial TB (Fig. 2A). At the genus level, Enterococcus, Escherichia coli (E. coli), and Mycoplasma were more prevalent in women with pelvic TB, whereas those with endometrial TB exhibited higher abundance of Gardnerella and Streptococcus (Fig. 2B). At the species level, increased abundance of E. coli, Enterococcus faecalis, and Ureaplasma parvum were observed in the vaginal microbiota of women with pelvic TB, whereas Gardnerella and Streptococcus were more abundant in the vaginal microbiota of women with endometrial TB (Fig. 2C).

LefSe analysis results indicated a significantly higher abundance of Actinomycetes, Streptococcus, and Finegoldia in the vaginal microbiota of women with endometrial TB (Fig. 3B). Dimension reduction analysis revealed significant dissimilarities in the vaginal microbiota of women with pulmonary TB compared with that in the other three groups. Additionally, the vaginal microbiota of women with pelvic TB and endometrial TB partly overlapped with that of healthy women, with the vaginal flora of women in the pelvic TB group showing the closest resemblance to healthy controls (Fig. 3A). KEGG functional analysis revealed that pathways such as ko03010 ribosome, ko00970 aminoacyl-tRNA synthesis, ko00230 purine metabolism, ko00240 pyrimidine metabolism, and ko00010 glycolytic gluconeogenesis were upregulated in the vagina of women with endometrial TB (Fig. 3C).

Discussion

Female genital TB remains a significant concern contributing to considerable morbidity, particularly infertility among women of reproductive age [18]. Most new TB cases, accounting for 87%, are concentrated in thirty countries with high TB burden. Notably, two-thirds of the total cases are reported in eight countries, with India leading the tally, followed by Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa [19]. Both TB itself and the prolonged duration of anti-TB treatment can influence the flora across various parts of the body. Numerous investigations have demonstrated alterations in gut microbiota among patients with active TB, with profound and long-term effects resulting from anti-TB medications [6].

While previous research on patients with TB predominantly focused on the intestinal and respiratory microbiota of those with pulmonary TB, limited attention has been directed toward the vaginal microbiota of women with genital TB. Notably, there exists a significant degree of similarity among bacterial phyla resident at different anatomical sites, albeit variations in the proportions of specific species [20]. Building upon this understanding, our study represents the first comprehensive analysis of the vaginal microbiota among Chinese women with pulmonary, pelvic, and endometrial TB. In this study, women of childbearing age were included for comprehensive screening and classification, with the diagnosis of pelvic and endometrial TB meticulously established through a combination of historical, symptomatic, imaging, surgical, and histopathological evidence. Consequently, the findings from our investigation are relatively reliable.

L. iners dominance is the characteristic of female genital TB

Our findings suggest the proportion of L. iners was higher than that of L. crispatus in women with genital TB. A healthy vagina typically exhibits low microbial diversity, often dominated by one or a few Lactobacillus species [21]. Mounting evidence suggests that the presence of L. iners constitutes an unfavorable factor for

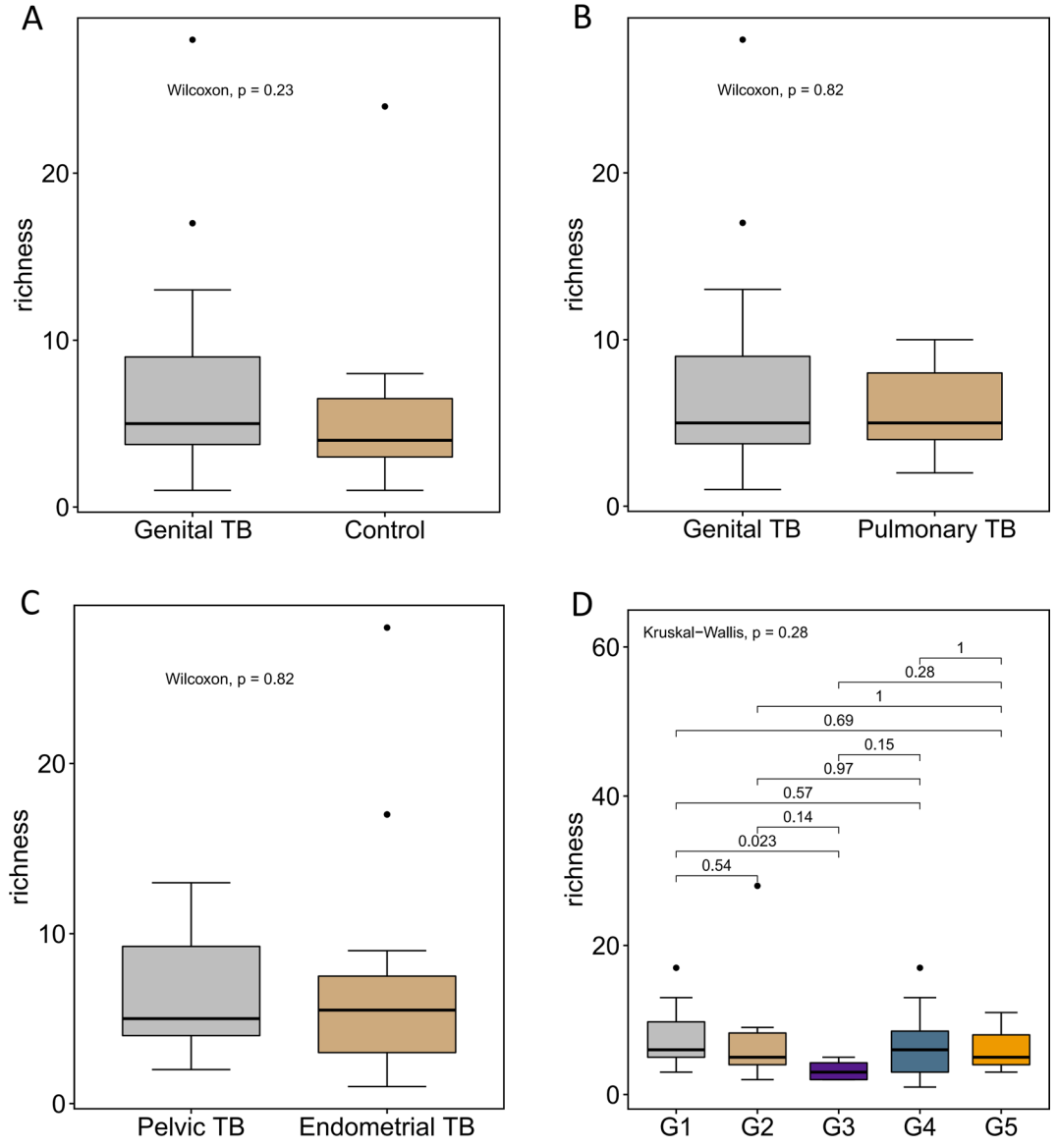

Fig. 1 Alpha diversity of vaginal microbiota in women with tuberculosis. **A**. Genital TB vs. Control, $P=0.023$; **B**. Genital TB vs. Pulmonary TB, $P=0.82$; **C**. Pelvic TB vs. Endometrial TB, $P=0.82$; D. G1, G2, G3, G4 and G5 respectively represented untreated, within 6 months of treatment, 6 months to 1 year of treatment, over 1 year of treatment, and drug withdrawal

pregnancy establishment [22]. L. iners is a transitional species that colonizes in disturbed vaginal environments, offering less protection against vaginal dysbiosis. Consequently, this can lead to conditions such as BV, sexually transmitted infections, and adverse pregnancy outcomes [23]. Unlike L. crispatus, L. iners cannot produce hydrogen peroxide and can only produce L-lactic acid because it lacks the gene responsible for encoding D-lactate dehydrogenase, thereby generating D-lactic acid, which exerts a more potent inhibitory effect on exogenous bacteria than that of L-lactic acid [23].

Anti-TB therapy affects the diversity of vaginal microbiota

The alpha diversity of the vaginal microbiota reaches its lowest point at six months to one year of anti-TB treatment, which is consistent with observations in the gut microbiota. Broad-spectrum antibiotic use reportedly disrupts both the composition and total abundance of the microbiota. After withdrawal of medication, the gut microbiota may either recover or establish a new balance [9]. Concordantly, we observed that the imbalance in vaginal microecology was most pronounced when M. tuberculosis invaded the endometrium. Probiotics have exhibited anti-TB activity in vitro and in vivo, suggesting their potential for application in anti-TB treatment to mitigate complications caused by the use of multiple

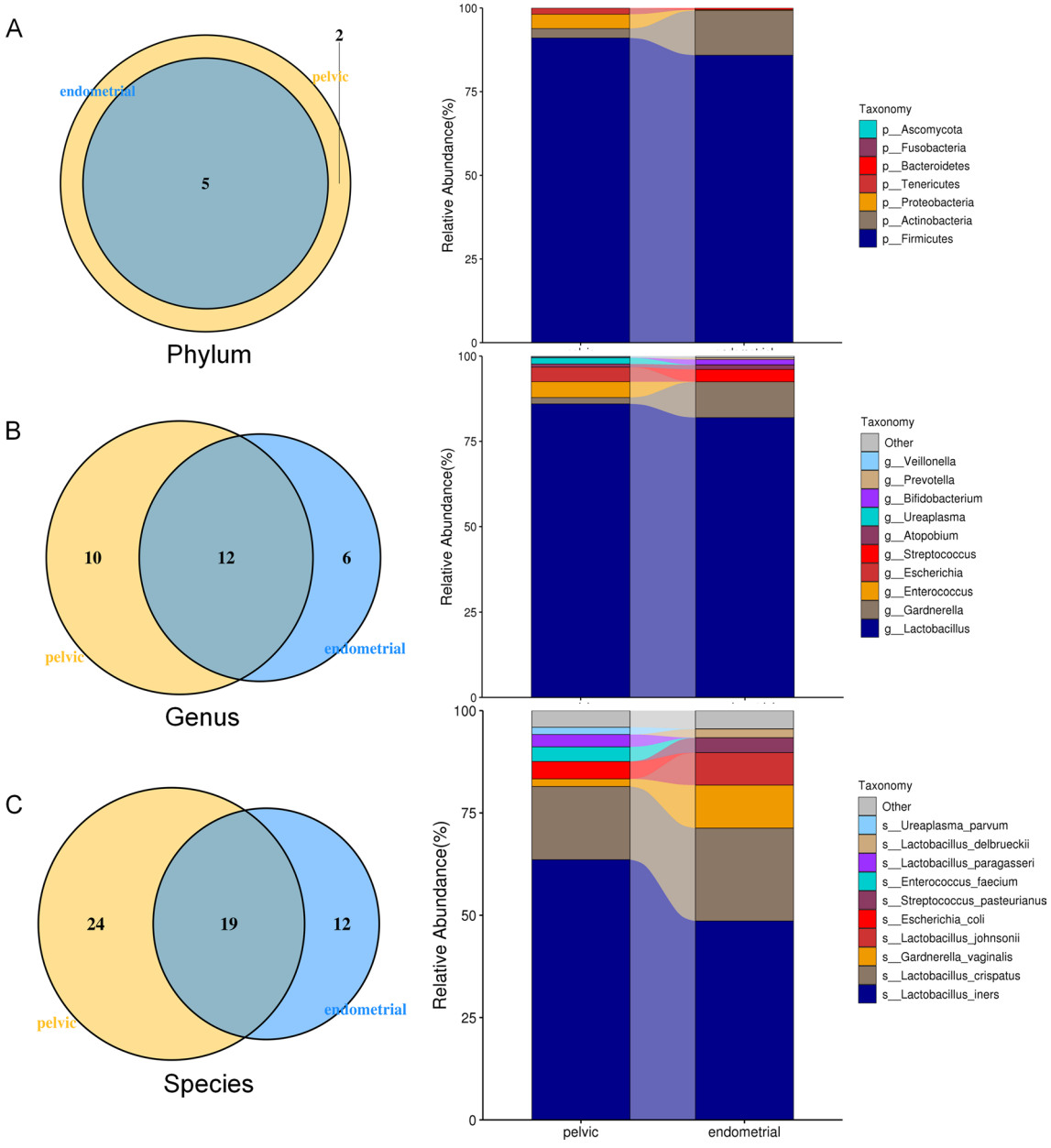

Fig. 2 Taxonomy of vaginal microbiota in women with pelvic and endometrial tuberculosis. **A**. Phylum level; **B**. Genus level; **C**. Species level

antibiotics [24]. In light of these findings, prebiotics, such as D-lactic acid produced by certain Lactobacillus strains, hold promise as adjunct therapeutics or optimization strategies for restoring homeostasis in the gut or genital tract, thereby potentially mitigating complications associated with prolonged antibiotic use during TB treatment.

SCFAs-producing bacteria and precursor pathways were up-regulated in endometrial TB

We have observed the abundance of Actinomycetes, Streptococcus, and Finegoldia in the vaginal microbiota is significantly higher in women with endometrial TB. Previous research on the respiratory flora in patients with TB revealed similar findings, with increased relative abundances of Streptococcus and Staphylococcus reported in pulmonary TB [25]. Finegoldia, also known as Peptostreptococcus, is an anaerobic gram-positive coccus, an opportunistic pathogen, and a component of prepubescent vaginal microbiota. Finegoldia can ferment polysaccharides and some amino acids to produce short-chain fatty acids (SCFAs), such as acetic and butyric acids [26, 27]. Streptococcus is also an acetic acid-producing bacteria [28]. SCFAs, including acetate, propionate, and butyrate, are bacterial products derived from commensal bacterial fermentation of dietary fibers in the intestine.

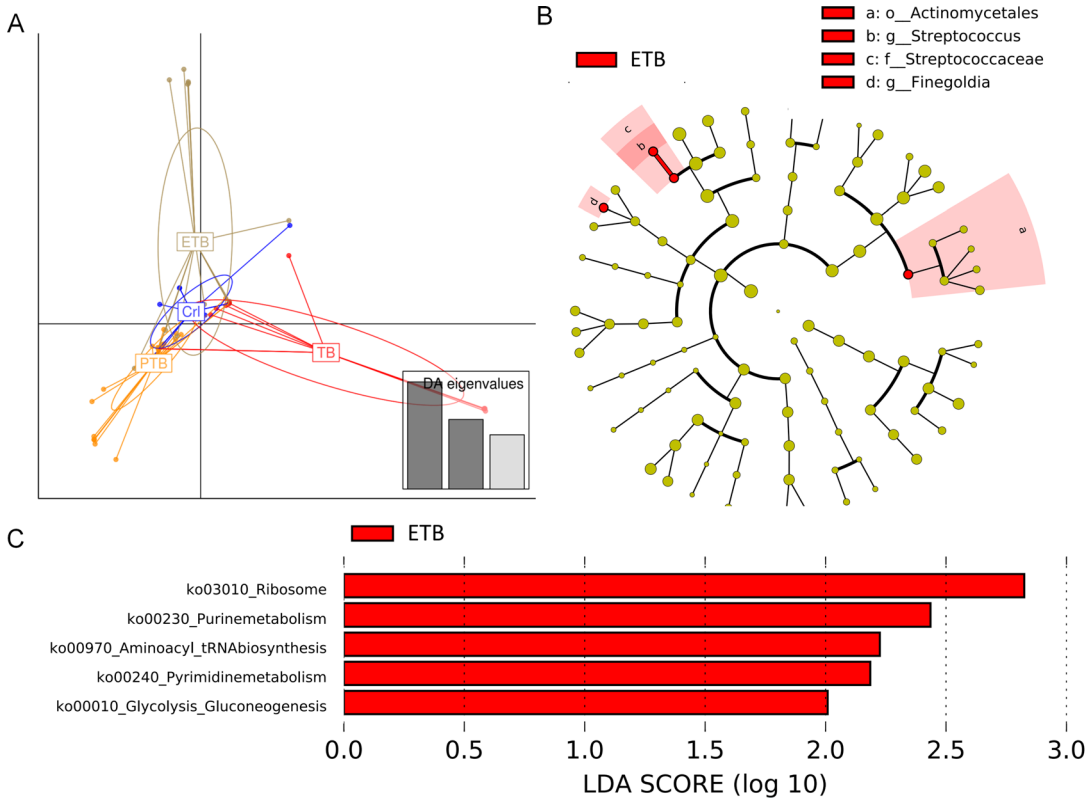

Fig. 3 Metagenomic analysis of vaginal microbiota in women with tuberculosis. **A**. Principal Coordinates Analysis (PCoA) based on Bray-Curtis distance; **B**. LEfSe linear discriminant analysis; **C**. KEGG differential analysis of metabolic pathways

They regulate cellular metabolism and exert potent immune-regulatory functions [29]. While the SCFAs maintain homeostasis and promote eubiosis in the gut, they induce dysbiosis and inflammation in the vagina, especially when the dominance of health-promoting Lactobacillus is compromised [28]. Lactic acid, primarily produced by Lactobacillus, maintains the vaginal pH at 3.5–4.5, thereby preventing the overgrowth and colonization of opportunistic pathogens [28]. An increase in vaginal SCFAs and concomitant decrease in lactate levels, as observed in BV, is a marker of dysbiosis as they increase the pH above 4.5, facilitating the overgrowth of mixed anaerobes [28]. Moreover, SCFAs are less anti-inflammatory than lactic acid, promoting inflammation by inhibiting neutrophil chemotaxis and increasing the production of pro-inflammatory cytokines [28].

Pathways associated with ribosome, aminoacyl-tRNA synthesis, purine metabolism, pyrimidine metabolism, and glycolysis gluconeogenesis (ko03010, ko00970, ko00230, ko00240, and ko00010, respectively) were all significantly upregulated in the vaginal microbiota of women with endometrial TB. The significantly upregulated metabolic pathways are all precursors of SCFA production [29], indicating vigorous metabolism and enhanced SCFA production in the vaginal flora of these women. Therefore, the increase in SCFA-producing anaerobes and the upregulation of SCFA precursor pathways in the vagina of women with endometrial TB are signs of vaginal microecological imbalance, and studies have shown that vaginal dysbiosis are associated with infertility [30].

Female genital tuberculosis deserves more attention because of its devastating effect on fertility. Our study also has some limitations due to the limited sample size. The intricate relationship and underlying mechanisms between the genital tract microbiota and infertility in women with genital TB remain to be fully elucidated. Additionally, the efficacy of probiotic therapy for women with genital TB requires further investigation to provide more ideas for the treatment and fertility protection of genital tuberculosis.

Conclusion

In conclusion, our findings provide comprehensive insights into the vaginal microbiota of Chinese women with genital TB, particularly endometrial and pelvic TB. We observed that the alpha diversity of the vaginal microbiota was at its lowest six months to one year into anti-TB treatment. L. iners-dominant vaginal microbiota was more prevalent in women with genital TB than in those with L. crispatus dominance. Women with genital TB, especially those with endometrial TB, exhibited

vaginal dysbiosis. Anti-TB treatment led to a reduction in the diversity of vaginal microbiota. Furthermore, we observed a significant increase in the abundance of SCFAs-producing anaerobes and upregulation of SCFA precursor metabolic pathways in women with endometrial TB.

In the context of global efforts to combat TB, our findings highlight the importance of considering extrapulmonary TB, particularly genital TB and its associated vaginal dysbiosis, which significantly impacts female fecundity. Future studies should focus on integrating longitudinal microbiota analyses with transcriptome and metabolome profiling to determine whether changes in the relative abundance of specific taxa translate into alterations in the concentrations of immunomodulatory metabolites, and probiotic combined interventions could also be used as a future research direction, which will lay the groundwork for the development of novel microbiological and immunotherapeutic strategies.

Methods

Study cohort and sample collection

The study was conducted in accordance with the Declaration of Helsinki and its current amendments, with approval from the medical ethics committee. Written informed consent was obtained from all participants. Women diagnosed with tuberculosis at Hebei Chest Hospital between July 2022 and December 2023 were included in the study cohort. This comprised 28 patients with pelvic TB, 16 with endometrial TB, and 12 with pulmonary TB. Additionally, 11 healthy women from the gynecological clinic of Beijing Obstetrics and Gynecology Hospital were included as the control group. Women without discomfort symptoms of lower reproductive tract or tuberculosis infection were selected as healthy controls. Vaginal discharges were collected from all participants during the middle of the follicular phase for microecological detection and metagenomic analysis of the vaginal microbiota.

Inclusion criteria comprised individuals being over 18 years old, having sexual experience, having a regular menstrual cycle (5–7/28–30 days), a normal body mass index (18.5–23.9 kg/m2), non-smokers, having a single sex partner, engaging in simple transvaginal intercourse, and having no recent history of genitourinary infections. Exclusion criteria included pregnancy, lactation, or menopause periods, recent antibiotic use within 7 days, sexual activity or vaginal douching within 7 days, long-term use of oral glucocorticoids or immunosuppressants, oral contraceptive use, and presence of chronic disease or malignant tumor.

Endometrial tuberculosis diagnostic criteria

The diagnostic criteria for endometrial tuberculosis [18] included ultrasonography (USG) findings such as a thin endometrium, endometrial fluid, calcification, or banded intrauterine adhesions. Additionally, typical tuberculous nodules observed in endometrial tissue biopsy, performed 1–2 days before menstruation or 12 h after menstruation, were considered. The absence of tubal tuberculosis was also required.

Pelvic tuberculosis diagnostic criteria

Diagnostic criteria for pelvic tuberculosis [18] included USG findings of hydrosalpinx with cogwheel signs in homogeneously enlarged ovaries with free peritoneal fluid and fixed adnexal masses. Tubal stiffness, beaded changes, fimbrial adhesion, and obstruction under imaging were considered. Tuberculosis bacilli found in abdominal effusion or pathogenic and histological evidence of tuberculosis found using laparoscopy were also indicative. Laparoscopic findings such as tubercles on the peritoneum or ovaries, tube-ovarian masses, caseous nodules, and encysted ascites, with no signs of endometrial tuberculosis in uterine curettage, were considered.

Pulmonary tuberculosis diagnostic criteria

Diagnostic criteria for pulmonary tuberculosis [31] included symptomatic presentation, positive sputum sample for Mycobacterium according to smear microscopy results, and absence of pelvic or endometrial tuberculosis from pelvic or peritoneal examination and curettage.

Sample collection

Participants meeting the aforementioned criteria and consenting to participation provided informed consent before sampling. Vaginal discharge was collected from each participant from the upper third of the lateral wall using two sterile cotton swabs. One swab was Gram-stained and observed using an oil lens (100×) for vaginal microbiological analysis, whereas the other was placed into a 2 mL Eppendorf tube containing normal saline and stored at − 80℃ for metagenomic sequencing of the vaginal microbiota.

Diagnosis of vaginitis

The following protocol was followed to diagnose vaginitis [32]. The Nugent score was adopted to diagnose bacterial vaginosis (BV) (a Nugent score of 7–10: BV; 4–6: intermediate BV; 1–3: normal). Vulvovaginal candidiasis (VVC) was diagnosed when hyphae or spores were found upon observation using an oil lens. No other types of vaginitis were found in this study. The number of white blood cells in vaginal secretions was evaluated by high

power field (HPF) and was distinguished as 0–5/HPF, 5–15/HPF, and > 15/HPF.

Metagenomic sequencing and microbiota analysis

Extraction of sample DNA, library construction, and sequencing

Sample DNA was extracted according to the protocol of the E.Z.N. ATM Mag-Bind Soil DNA kit (OMEGA). DNA integrity was assessed via agarose gel electrophoresis. Qualified DNA samples were randomly fragmented to approximately 350 bp using an ultrasonic crusher (Covaris). Following end repair, the library was constructed by adding an A tail and sequencing adapter, followed by purification and PCR amplification. Preliminary quantification was performed using a Qubit 3.0 fluorometer, and the library was diluted to a concentration of 2 ng/μL. The library insert size was determined using an Agilent 2100 Bioanalyzer, and the effective library concentration was accurately quantified using qPCR (effective concentration > 3 nmol/L). The qualified library was sequenced on an Illumina Novaseq sequencing platform.

Bioinformatic analysis

Quality control measures included: (1) removal of reads with low-quality bases (quality score < 20) exceeding the specific length threshold (40 bp); (2) trimming of reads with an N base length exceeding the specific threshold (10 bp); (3) removal of reads overlapping with the adapter exceeding the specific threshold (15 bp); and (4) filtering out reads potentially originating from the host not found in the host database using Bowtie2. MetaPhlAn2 was utilized for species annotation, with relative species abundance calculated at each taxonomic levels. For each sample or group, a histogram of relative abundance and a Venn diagram were generated for species ranking in the top 10 at each classification level. Species with abundance ranking > 10 were categorized as "others."

Statistical analyses

Statistical analyses included: (1) alpha diversity analysis to assess species diversity within individual samples or groups; alpha diversity increases with a higher number of species, indicating greater richness within the sample or group; (2) Linear discriminant analysis effect size (LEfSe) analysis to identify statistically significant biological markers between groups, represented in a circular evolutionary tree; (3) Principal Coordinates Analysis (PCoA) for dimension reduction analysis, visualizing data similarities or differences based on Bray–Curtis distance. Following the sorting of eigenvalues and eigenvectors, the principal coordinates in the distance matrix were identified by selecting the first few eigenvalues, enabling the observation of differences between individuals or groups through PCoA. 4); (4) Kyoto Encyclopedia of Genes and Genomes (KEGG) functional analysis to identify differentially expressed bacterial metabolites or signaling pathways; and (5) general statistical analysis conducted using SPSS 19.0 software, with analysis of variance (ANOVA) for age comparison and Chi-square or Fisher exact test for other comparisons, as presented in Table 1. Statistical significance was denoted by $P < 0.05$.

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Author contributions

ZZ participated in the study design, literature search, specimen collection, data analysis and manuscript writing. XZ analyzed and interpreted the patient data and participated in manuscript writing. XD participated in the study design and patient recruitment, manuscript editing and revisions. LF, HB and TL provided help in the literature search and specimen collection. ZL participated in the study design, patient recruitment, specimen collection, data analysis, manuscript editing and manuscript review. All authors have read and approved the final manuscript.

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Data availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All participants provided their informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Beijing Obstetrics and Gynecology hospital, Capital Medical University (2022-KY-064-01).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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