

# Female genital tuberculosis: the neglected history of a neglected disease and its implications for women's health

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## Keywords

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## Summary

*Female genital tuberculosis (FGTB) is a rare but significant form of extrapulmonary tuberculosis that is associated with infertility and gynaecological morbidity, particularly in low-income countries. Although this disease is clinically recognised, it has been neglected in the past both in clinical research and in scientific historiography. Our study analyses the evolution of knowledge about FGTB, from the first anatomical-pathological description by Giovanni Battista Morgagni in 1744 to the most recent diagnostic and therapeutic achievements. The historical analysis shows how interest in FGTB has only accelerated since the late 19th century, with important contributions from clinicians such as Ernesto Pestalozza and Arthur M. Sutherland, who promoted a*

*modern approach to diagnosis through histological, bacteriological and radiological investigations. Despite advances in imaging and molecular biology techniques, FGTB still poses a diagnostic challenge due to the non-specific clinical presentation and paucibacillary nature of the disease. Manifestations often lead to late diagnosis, the reason why it represents a paradigmatic example of how a disease can remain largely invisible despite its consequences for individual and public health. We believe that FGTB should be recognised as a neglected infectious disease with clinical, epidemiological and historical implications. Its scientific and historical rediscovery can stimulate further studies and an integrated approach to women's health.*

## Background, aims and methods

Tuberculosis (TB) is an airborne infection caused by organisms of the *Mycobacterium tuberculosis complex* and usually affects the lungs. However, *M. tuberculosis* can cause disease in almost any part of the body. Extrapulmonary manifestations therefore include: spondylodiscitis, meningitis, gastroenteritis, urinary tract infections and genital tuberculosis. The latter is a neglected disease that nowadays occurs mainly in low-income countries and can affect both female fertility and neonatal outcomes [1]. Female genital tuberculosis (FGTB) is an important cause of morbidity worldwide, with many patients having an indolent disease which is often only diagnosed after an investigation for infertility [2]. Communicable and neglected gynecological conditions are often underreported, misdiagnosed, and as a consequence largely untreated [3]. Moreover, FGTB has never been reviewed in the history of medicine and science.

The aim of the article is to briefly describe the disease and summarise the most important scientific discoveries about FGTB in the history of medicine since the first documented written description by Giovanni Battista

Morgagni in 1744. The paper will provide a new perspective on a disease that has been neglected in the history of science and still carries a significant morbidity burden today. Scientific databases (e.g. PubMed and Google Scholar) and historical records have been reviewed, including *De sedibus et causis morborum* English translation by Benjamin Alexander, 1769.

## Female genital tuberculosis

*Mycobacterium tuberculosis complex* comprises several closely related species, with *M. tuberculosis* being the most important one that infects humans [4]. While *M. tuberculosis* is the main cause of TB worldwide, other species like *M. africanum* and *M. bovis* can also infect humans. The lipid-rich, hydrophobic cell wall of *M. tuberculosis* contributes significantly to its resistance to the host's immune defences and many antimicrobial agents [4].

Among the extrapulmonary manifestations of TB, FGTB is a rare manifestation that leads to infertility. In fact, infertility is the most common manifestation, affecting 60-80% of women with FGTB. This is primarily due

to obstruction or deformation of the fallopian tubes, intrauterine adhesions or damage to the ovarian tissue leading to a reduced ovarian reserve. Primary infertility (never having been pregnant before) is more common than secondary infertility (having been pregnant before) and accounts for 66%-85% of infertility cases in women with FGTB. In many patients, the diagnosis is only made after infertility testing, which indicates the indolent nature of the disease [2]. Approximately 40% of women with FGTB may be asymptomatic, making diagnosis difficult. Chronic abdominal and pelvic pain is frequently reported, often accompanied by menstrual irregularities, dysmenorrhoea or postmenopausal bleeding. Symptoms such as dyspareunia and abnormal vaginal discharge may also be present [5]. Approximately 35-50% of patients with FGTB may have a completely normal physical examination, which means that the absence of abnormal signs does not rule out the disease. In cases where abnormal findings are present, they may be vague and not correlate well with the patient's symptoms. These typically include adnexal masses or signs of ascites, which may indicate more severe disease. In menopausal women, FGTB may result in an enlarged, tense and tender uterus due to the formation of a pyometra, which may mimic other conditions such as endometrial cancer or gynecological malignancies. Physical examination

may reveal vaginal fistulas; moreover fistulous tracts can be present between the genital tract and adjacent organs such as the bowel or bladder, often due to complications such as rupture of a tuberculous pyosalpinx [6].

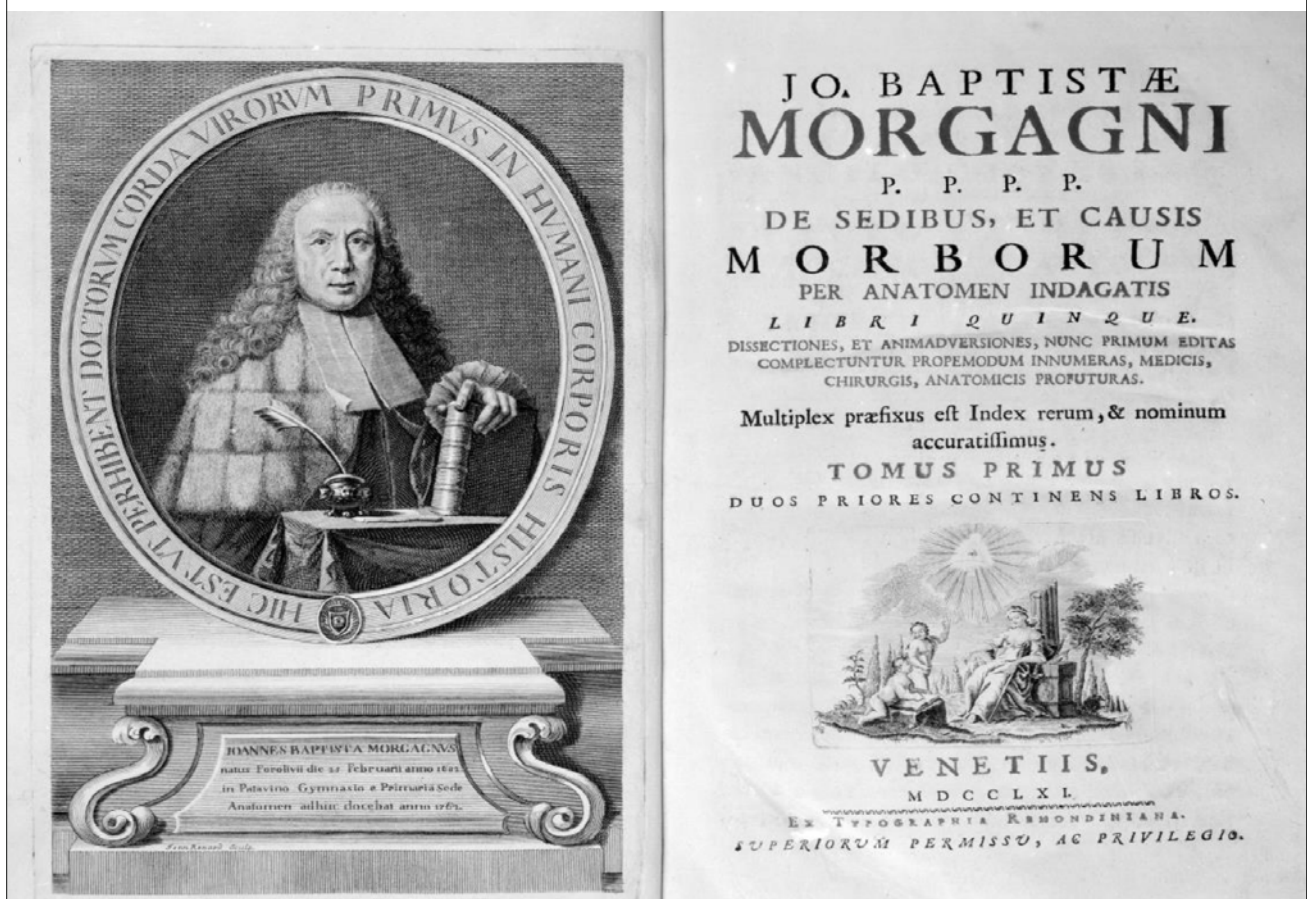
Due to its clinical presentation, FGTB can be misdiagnosed as a chronic pelvic inflammatory disease (PID) or even as a malignant disease such as ovarian and uterine cancer, as the symptoms overlap. Elevated serum CA-125 levels, which are often associated with malignancy, may also be elevated in FGTB, further complicating the diagnostic process [2, 5].

From an anatomopathological point of view, FGTB typically presents with granulomatous inflammation, which is characteristic of TB infection. In the endometrium, 46.7% of cases showed well-formed multicentric granulomas with varying degrees of caseous necrosis, indicating active infection. Granulomas can occur at different stages. The ovaries have the highest rate of acid-fast bacilli, followed by the fallopian tubes, endometrium and cervix [7].

### The first written description of FGTB

It is widely accepted that the first reported FGTB was seen by Morgagni in the year 1744 and detailed in *De Sedibus et Causis Morborum* (Fig. 1), Letter XXXVIII,

**Fig. 1.** G.B. Morgagni, "De sedibus et causis morborum per anatomen indagatis", 1761. Wellcome Images (<http://catalogue.wellcomelibrary.org/record=b1204928>). Wikimedia Commons.



Number 34 [8, 9]. In the manual he reports about a: “*virgin of twenty years [...] having had no [...] menstrual discharges, for two years*”. The girl, before reaching the hospital of Padua, complained about “*pains*” and “*the belly began to be tumid. [...] for about a year*”. Moreover, he reports the patient complaining “*a slight fever, [...] fetid, and liquid, stools*”. After the symptoms description, Morgagni states “*she died about the middle of December, in the year 1744*”.

When describing the autopsy scan the first characteristic reported is cachexia: “*The body was emaciated*”. Later he writes about pathological findings of the abdomen: “*belly was very large, but not tense*”. As a consequence, he started the scan from there “*[...] being perforated at one side, a great quantity of water was gradually discharg’d [...] yellowish, and thin; the other less thin, and almost white. But when I examin’d [...] after [...] twenty-four hours, in a very large vessel [...] was pretty thick [...] pieces of the omentum being mix’d with it [...] neither the water, nor the body, had a putrid smell*” [10]. In the following pages he describes the inflammatory process of the peritoneum and the extension of the disease to the right and left hypochondriac region: “*The whole of the omentum [...] was torn into pieces [...] The liver [...] coher’d with the diaphragm [...] The spleen [...] was preternaturally increas’d [...] The same appearances were observ’d, here and there, on the interior surface of the peritoneum, and on the exterior of the intestines, especially of the small ones, in which, likewise, were hydatids. The largest of these was equal to the size of a small apple*” [10].

After this general description Morgagni’s move to adnexal organs and pelvis focusing on the “*peculiar disorder in the testes, the tubes, and the uterus itself*”. He reports about the macroscopic appearance of the

inflammatory process and the caseous material filling the uterus and fallopian tube. He reports the disease: “*was not discover’d in the uterus, without dissection; but in the testes, and the tubes, came spontaneously into view. For these parts had, equally on both sides [...] grown into a kind of tuberous, and shapeless mass, of a considerable size, that one could not, by any means, be known from the other [...] The surface of each of these masses was lacerated, for a considerable space, and was found to be spontaneously open*”. Interestingly, he follows describing the characteristics of the pelvic process: “*it consisted of a matter, which resembled nothing more than half-dried fuet: so white was it; of so unctuous a nature [...] it was quite inodorous*”. He proceeded to dissect the uterus with these words: “*when I cut pretty deeply into the fundus of the uterus [...] I saw that the remaining internal part of the substance [...] was converted into a matter which was similar to that just now describ’d*”. He writes the “*same matter the cavity of the fundus was filled [...] fall through the cervix, into the vagina, which was even now whitish, from the remains of this very matter*” [10].

As shown above, Morgagni’s first written description of a case of FGTB summarises most of the features of the disease, such as: tumour-like masses with caseous material, anatomical disruption of normal genital anatomy, peritoneal ascites, splenomegaly and vaginal discharge.

## Main discoveries on FGTB in the following centuries

In 1857, Namias published a study full of observations on FGTB [11] and two years later, Calza gave a very accurate description of genital tuberculosis in a little girl. However, only in the late 1800s and early 1900s, research into FGTB started to be widespread. This disease was discussed at the International Congress in Rome in 1902 and in Munich in 1911 (Jung and Kronig) in relation to pregnancy. A fundamental contribution was later made by Italian clinicians. Ernesto Pestalozza (1860–1934), depicted in Figure 2, confirmed his extensive knowledge of the subject at the Congress of the Italian Society of Obstetrics and Gynaecology in 1921 [12]. “*Genital tuberculosis in infancy and prepuberty is far more common than is generally assumed*”, concluded Pestalozza in 1921 on the basis of his own anatomical and clinical observations and on the basis of an extensive world literature. He therefore considered it useful to spread awareness among general practitioners and paediatric specialists of such disease, not least because local forms of tuberculosis may leave after-effects whose influence may be largely felt in the woman’s subsequent sexual life [13].

As far as the treatment of FGTB is concerned, various invasive surgical techniques have been introduced since the late 19th century, together with heliotherapy, iodine therapy and serotherapy [12]. Interestingly different authors of the early 20th century advocated against

**Fig. 2.** Roberto Fantuzzi, “Ernesto Pestalozza and disciples”, 1934. Policlinico Umberto I in Rome. Courtesy by Policlinico Umberto I.



**Fig. 3.** Royal Samaritan Hospital and Southern General Hospital, where Arthur M. Sutherland worked. Both retrieved from Wikimedia Commons (attribution for the second image: wfmillar / Southern General Hospital / CC BY-SA 2.0.).



heliotherapy and conservative treatments in favour of surgery in genito-urinary TB [14].

A major contribution to FG TB was later made by Arthur M. Sutherland in 1944. The author wrote a thesis for his degree which was a case series and a literature review on the topic. Interestingly, he reported that the diagnosis was based solely on the histopathological examination of the endometrium and was supplemented by a bacteriological examination. He also wrote on the surgical and radiological examinations used. For example, dilation of the cervix and curettage of the uterus (with or without endometrial biopsy) were advocated. Tubal insufflation techniques and X-ray examinations were also well described [15]. Sutherland started to work in the Department of Obstetrics and Gynaecology at the Royal Samaritan Hospital and the Southern General Hospital in Glasgow (Fig. 3). Between 1 January 1950 and 15 June 1978, 638 women with proven tuberculosis of the genital tract were examined and monitored by the authoritative author. He reported that the treatment of choice at the time was a combination of rifampicin, ethambutol and isoniazid for 1 year. However, 7 different drug regimens were used to treat 581 patients. Apart from the most recent therapies, the best results were achieved with a combination of streptomycin, para-aminosalicylic acid and isoniazid for 18 months or 2 years. Interestingly, he stated that surgery should be performed if drug treatment failed [16]. Among other important publications in this field in the middle of the 20th century are those by Bret and Legros (1956), Ehrler (1966), Jameson (1935), Jedberg (1950), Ryden (1953), Schaefer (1956), ten Berge (1964) and Ylinen (1960). Each of these authors provides a detailed overview of the literature [12, 16].

### Current state of the art

The nonspecific and often misleading clinical presentation of FG TB leads to frequent underdiagnosis and uncertainty regarding its true prevalence. Its occurrence is strongly associated with the prevalence of

pulmonary tuberculosis, ranging from less than 0.1% in the high-income countries to nearly 20% in India [8]. A recent meta-analysis considering different World Bank country income classification estimated the pooled prevalence of female genital tuberculosis (FGTB) at 20%. Among women with FGTB, the prevalence of overall infertility, primary infertility, and secondary infertility was 88%, 66%, and 34%, respectively [17]. FGTB is more commonly observed in low-resource settings, where HIV infection, immunosuppression, and limited access to healthcare act as additional risk factors [18, 19].

The condition primarily affects women of reproductive age and is frequently identified during infertility investigations [7]. Imaging modalities such as ultrasound, computed tomography, or magnetic resonance imaging may suggest FGTB when features like adhesions, calcifications, fibrosis, or abnormalities in endometrial thickness are present [20]. As with other forms of tuberculosis, definitive diagnosis requires the isolation of *M. tuberculosis* through culture, microscopic identification of acid-fast bacilli or PCR-based molecular assays. However, due to paucibacillary nature of FGTB, the microbiological confirmation is often difficult [8]. Histopathological examination, particularly the identification of caseating granulomas with multinucleated giant cells, provides additional diagnostic support [19]. Samples for microbiological and histopathological analysis are usually collected during hysteroscopic examination; hysterosalpingography as well is a key procedure in infertility assessment. Laparoscopy may also serve as a complementary or alternative tool [18]. While smear and culture of menstrual blood have been explored as a diagnostic option, their sensitivity remains low [21].

In cases of suspected FGTB, a comprehensive evaluation is essential to exclude TB involvement of other organs, with chest radiography routinely performed.

Overall, the diagnosis remains challenging and requires a high index of clinical suspicion, as FGTB is often misidentified as malignancy [18].

The treatment mirrors that of pulmonary tuberculosis

in terms of drug selection and total duration: 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid, rifampicin; often continuing to include pyrazinamide as part of the regimen (2HRZE/4HRZ) [22]. Drug-resistant cases follow specific guidelines. Surgery plays a role in severe cases, where abscesses drainage or adhesions breaking is needed [23, 5].

## Discussion

FGTB poses a major clinical and diagnostic challenge, especially in low-income areas where tuberculosis is endemic. Unfortunately, many patients have an indolent disease which is often only diagnosed after an investigation for infertility. However, the importance of this disease has been underestimated in the past, both scientifically and clinically. In our opinion, FGTB should be considered a neglected infectious disease in daily clinical practice as much as in the history of medicine. Morgagni's description of a case of FGTB in 1744 summarises most of the features of the disease, focusing mainly on the anatomical disruption of the female genital tract and the presence of tumour-like masses. From the first documented description of macroscopic signs suggestive of FGTB to the contributions of scientists such as Pestalozza and Sutherland (Fig. 4), a slow but significant development of knowledge

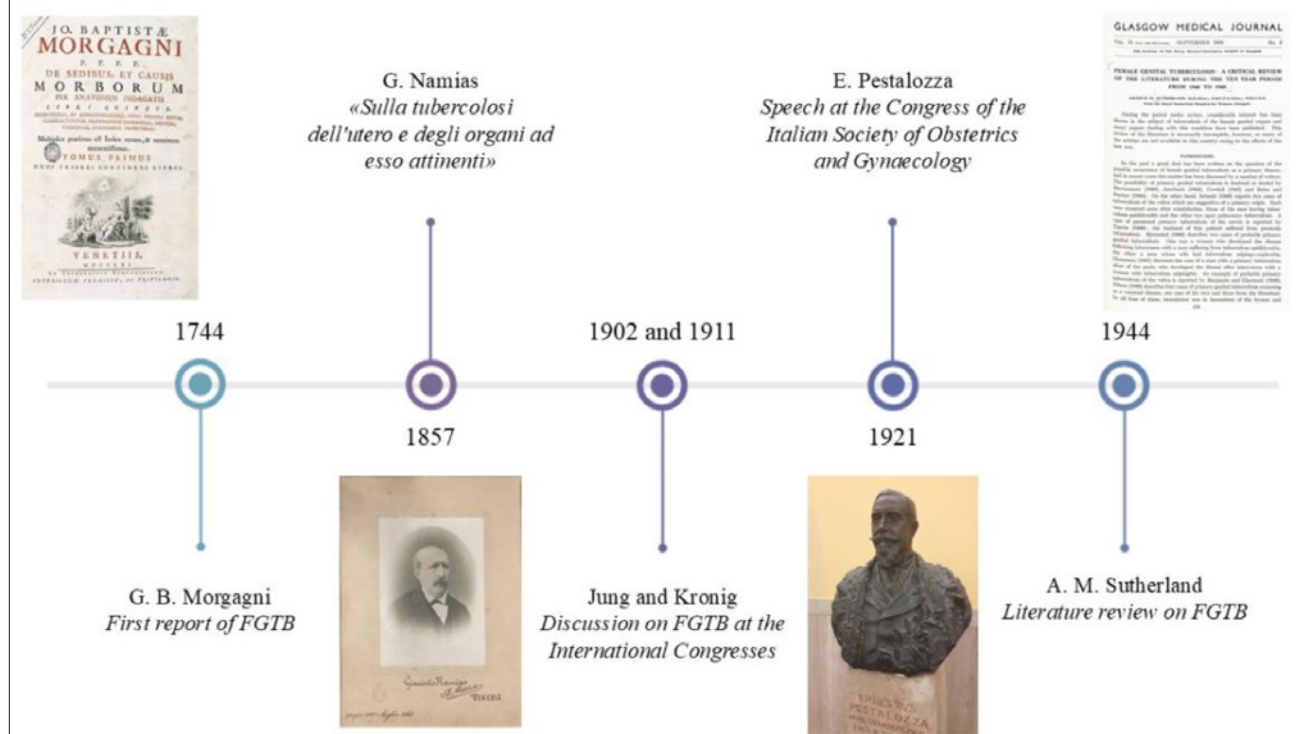
about FGTB can be observed; mainly since the late 19<sup>th</sup> century. Sutherland's work in particular provided a methodological framework for diagnosis based on histopathological, bacteriological and radiological examinations, some of which are still used today, albeit with modernized techniques.

Despite these advances, diagnosis remains problematic. The paucibacillary nature of the disease, the frequent absence of specific symptoms and the clinical overlap with other gynecological diseases make early identification difficult. Modern diagnostic tools such as PCR molecular techniques, advanced imaging and laparoscopy have increased sensitivity, but the index of clinical suspicion remains crucial. From a therapeutic point of view, the early attempts of heliotherapy, iodine therapy and serotherapy have given way to modern antitubercular therapies similar to those used in the pulmonary form (2HRZE/4HRZ). However, the clinical response can be variable and in some cases surgery is required to treat complications such as tubal abscesses or extensive adhesions.

## Implications for women's health

Female genital tuberculosis (FGTB) represents a paradigmatic example of how a disease can remain largely invisible despite its potentially deep consequences for individual and public health. Although tuberculosis is

**Fig. 4.** Timeline of main achievements in the study of FGTB since the first documented report. Original image (created by the authors with BioRender Image and Illustration Software) adapted from: Morgagni de sedibus 1761 (Wikimedia Commons), Portrait photograph of G. Namias (held in the Historical Archive of the Istituto Veneto di Scienze, Lettere ed Arti), Photo of E. Pestalozza (for Himetop – The History of Medicine Topographical Database) and SUTHERLAND AM. Female genital tuberculosis: a critical review of the literature during the ten year period from 1940 to 1950. Glasgow Med J. 1950 Sep;31(9):279-95. PMID: 14778522; PMCID: PMC5970847.



often perceived as a disease of the past or as a condition primarily affecting the lungs, its extrapulmonary forms continue to pose important diagnostic and therapeutic challenges. Among these, FGTB is particularly meaningful because of its impact on reproductive health, fertility, pregnancy outcomes, and psychosocial well-being.

The persistence of FGTB in the twenty-first century features the complex interplay between infectious diseases, social determinants of health, and gender-related disparities in healthcare. In many settings, women affected by FGTB experience delayed diagnosis due to the nonspecific nature of symptoms, limited awareness among healthcare providers, and barriers to accessing specialized care. As a result, the disease frequently goes unrecognized for extended periods, delaying diagnosis and treatment. Consequently, many patients are diagnosed only at advanced stages of the condition, when substantial and often irreversible damage to the reproductive tract has already occurred.

FGTB offers an important lens through which to examine the principles of gender medicine. Historically, many aspects of women's health have received less scientific attention than conditions affecting the general population or predominantly male cohorts.

We believe that this “diagnostic invisibility” not only delays appropriate treatment but also increases the risk of severe long-term consequences, including infertility, chronic pelvic pain, and psychological distress.

Addressing this gap requires healthcare systems and research plans to adopt a more gender-sensitive approach, one that recognizes the unique manifestations of disease in women, prioritizes timely diagnosis, and ensures equitable access to care and scientific attention. The historical and scientific rediscovery of FGTB therefore extends beyond the study of a single disease. It encourages reflection on how medical knowledge is generated, which diseases attract scientific attention, and which patient populations may remain underserved.

Revisiting the history of FGTB reveals how changing epidemiological patterns, diagnostic technologies, and social attitudes toward women's reproductive health have shaped our current understanding of the disease. Addressing the persistent challenges associated with FGTB requires a truly multidisciplinary effort involving gynecologists, infectious disease specialists, microbiologists, pathologists, epidemiologists, public health professionals, and experts in gender medicine. Such collaboration is necessary to close existing knowledge gaps, improve epidemiological surveillance, and develop more accurate and accessible diagnostic strategies.

Furthermore, greater awareness among clinicians and policymakers can promote earlier recognition of the disease and facilitate timely intervention.

Increased investment in research on FGTB may not only improve prevention and treatment strategies but also contribute to a more comprehensive understanding of the relationship between infectious diseases and women's health. In this sense, FGTB serves as a reminder that

diseases affecting reproductive health should not be viewed as niche conditions, but rather as important components of global health and social well-being.

Finally, integrating historical perspectives, modern scientific advances, and the principles of gender medicine can help transform FGTB from a neglected condition into a recognized public health priority. Such an approach has the potential to reduce diagnostic delays, preserve reproductive health, improve quality of life, and promote a more equitable and inclusive model of healthcare for women worldwide.

## Conclusion

FGTB remains a neglected condition with major consequences for women's reproductive health. Earlier diagnosis and a gender-sensitive multidisciplinary approach are essential to reduce its burden. History may help to recognize FGTB as a global health priority and promote equity in women's healthcare.

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## Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Authors' contribution

OS, SDB: designed the study. OS, AST, VG, MCDS, LZ, VZ, MM: drafted the manuscript. OS, AST, VZ, MM: performed a search of the literature. OS, AP, MM: data curation. AP, MCDS, LZ, MM, SDB: revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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