

# SILENT TUBERCULOUS ENDOMETRITIS AS A CAUSE OF PRIMARY AMENORRHEA IN A YOUNG WOMAN FROM A TUBERCULOSIS ENDEMIC COUNTRY: A CASE REPORT

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## ABSTRACT

**INTRODUCTION:** Tuberculosis (TB) is an infectious disease that primarily affects the lungs but can also involve genital organs and the endometrium. Endometrial TB generally has nonspecific clinical manifestations, such as menstrual irregularity causing amenorrhea and infertility.

**CASE PRESENTATION:** A 20-year-old nulliparous patient presented with primary amenorrhea of 20 years. She had no other complaints. She had no response to a 3-month treatment with combined oral contraceptives. Her medical history included a previous TB treatment at age 12. Clinical examination showed appropriate secondary sexual development. Laboratory tests, including thyroid, FSH, LH, estrogen, prolactin, and karyotyping, were normal. MRI revealed a hypoplastic uterus with intraluminal lesions, suggesting uterine synechiae and minimal hematometra. Hysteroscopy and laparoscopy confirmed extensive uterine synechiae and abdominal adhesions. A positive Interferon Gamma Release Assay (IGRA) indicated genital tuberculosis.

**CONCLUSION:** This case highlights the rare occurrence of tuberculosis-related uterine synechiae leading to primary amenorrhea, emphasizing the importance of considering tuberculosis in the differential diagnosis of unexplained primary amenorrhea in TB-endemic regions.

**KEYWORDS:** Tuberculous endometritis, amenorrhea, uterine synechiae.

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## INTRODUCTION

Tuberculosis (TB) remains a persistent global health issue, with Indonesia ranking as the country with the second-highest TB burden worldwide<sup>1</sup>. Tuberculosis is primarily caused by *Mycobacterium tuberculosis* infection, which primarily affects the lungs but can also involve other systems, including the genital and reproductive organs<sup>2</sup>. Genital TB typically originates from pulmonary TB that spreads to the genital tract through hematogenous or lymphatic dissemination<sup>1</sup>. The most commonly affected sites are the fallopian tubes (95-100%), uterine endometrium (50-60%), ovaries (20-30%), cervix (5-15%), uterine myometrium (2.5%), and vagina/vulva (1%)<sup>3</sup>.

Endometrial TB, a form of genital TB in women, has nonspecific clinical manifestations and is often overshadowed by pelvic TB. It typically affects reproductive-age women (15-40 years old) and is rarely diagnosed in children, partly due to low clinical awareness of the disease and its nonspecific symptoms<sup>1</sup>. While many patients are asymptomatic, others present with menstrual irregularities or infertility<sup>4</sup>. In advanced stages, adhesions between the ovaries can occur, and intrauterine adhesions may cause partial or complete obliteration of the uterine cavity, potentially leading to amenorrhea<sup>3</sup>. However, there are currently no reported cases of endometritis tuberculosis resulting in primary amenorrhea. Herein, we report a rare case of primary amenorrhea in a young woman with tuberculous endometritis.

## CASE PRESENTATION

A 20-year-old nulliparous patient presented to the endocrine clinic in Sardjito Hospital with a failure to menstruate since birth. The patient had undergone three cycles of combined oral contraceptives without achieving menstruation. She reported no lower abdominal pain, vaginal discharge, or abnormal hair growth on the chest and face. There were no complaints of headaches, projectile vomiting, persistent cough, weight loss, or weight gain. The patient reported no history of learning

or social adjustment disorders, dietary restrictions, medication use, sexual activity, or psychological stress. History-taking revealed that the patient had been diagnosed with pulmonary tuberculosis at age 12 and had completed a 6-month regimen. At age 13, she developed a mass on her left middle finger, which was biopsied. A pathology examination supported the diagnosis of cutaneous TB. She had undergone another course of TB medication and reported no signs or symptoms of pulmonary or extrapulmonary TB afterward.

On general examination, the patient had a body mass index of 18.73 kg/m<sup>2</sup> and normal vital signs. Head, neck, and lung physical examinations were unremarkable. Abdominal examination found no pain or palpable mass. Other systemic examinations were normal. Secondary sexual characteristic development was appropriate for age. Genital examination revealed an intact hymen and vagina. Subsequent uterine sounding measured the endometrial cavity at 4 cm in length.

Laboratory investigations showed a follicle-stimulating hormone (FSH) level of 6.89 mIU/mL, luteinizing hormone (LH) level of 9.66 mIU/mL, and estradiol level of 87.9 pg/mL, consistent with normogonadotropic normogonadism. Thyroid function tests were normal, with a thyroid-stimulating hormone (TSH) level of 2.53  $\mu$ IU/mL and free T4 level of 1.32 ng/dL. The prolactin level was 12.9 ng/mL, within the normal range. A chest X-ray revealed no lung abnormalities.

Radiological evaluation with transanal ultrasonography (USG) showed a normal uterus measuring 6.17 x 2.52 cm, with a possible impression of hematometra. Transperineal USG indicated normal anatomy of the urethra, vagina, rectum, and anal sphincter muscles. Magnetic resonance imaging (MRI) revealed a normal uterus measuring 3.2 x 6.4 cm with intraluminal lesions along the uterine cavity measuring 1.16 cm longitudinally. Uterine synechiae with minimal hematometra was suspected (**Fig 1**).



Fig 1. Pelvis MRI with contrast showed a normal uterus with minimal hematometra. In the distal uterus, a narrowing with intrauterine synechiae was seen (green arrow).

No abnormalities were detected in the parametrium or the kidneys. Karyotyping confirmed a normal 46, XX karyotype.

Based on history, physical examination, and supporting examinations, we established a working diagnosis of primary amenorrhea due to uterine hypoplasia with suspected synechiae uteri. The patient was then scheduled for hysteroscopy and diagnostic laparoscopy. Intraoperative hysteroscopy revealed fibrotic tissue covering the uterine cavity, obscuring visualization of the uterine corpus and fundus (Fig 2).

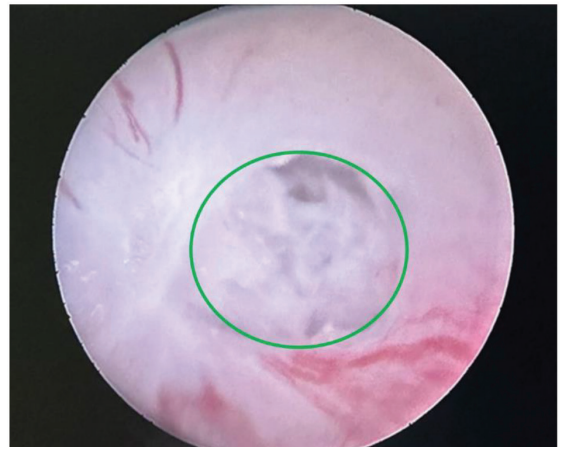
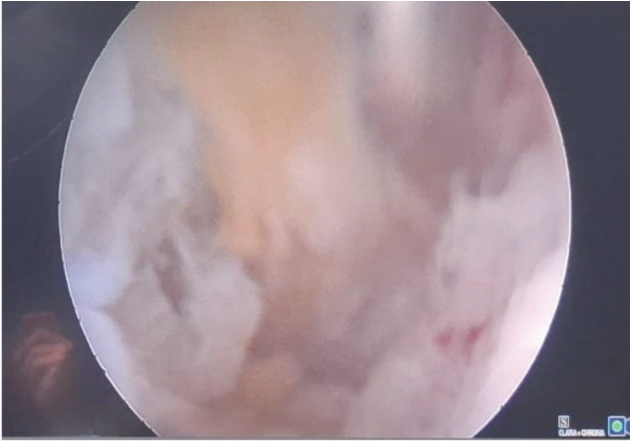


Fig 2. Hysteroscopic images revealed complete fibrosis of the uterine cavity. During the procedure, after passing through the external cervical canals, the hysteroscope could not pass through the internal cervical ostium. The uterine corpus and fundus could not be visualized due to total fibrosis (highlighted in the green circle).

Visualization of the fallopian tubes was also challenging. Laparoscopic examination showed extensive adhesions in the abdominal cavity between the intestines, omentum, and anterior abdominal wall, as well as between the uterus, pelvic cavity, and lateral pelvic wall.

Synechiolysis and adhesiolysis were performed, and a pathological examination of uterine and abdominal tissue samples confirmed chronic inflammation. The patient was then consulted with the pulmonology department, and the Interferon Gamma Release Assay (IGRA) test revealed positive results, while the Human Immunodeficiency Virus (HIV) test showed negative results. The patient then began a six-month course of treatment for extrapulmonary TB.

After completing TB treatment, the patient underwent a second-look hysteroscopy. The hysteroscope successfully accessed the uterine cavity, but fibrotic tissue was still present. Synechiolysis and adhesiolysis were performed to address the intrauterine adhesions (Fig. 3).



**Fig 3.** Hysteroscopic view during the second procedure following prior treatment. The cervical canal was accessed, revealing complete adhesions within the uterine cavity. Synechiolysis was performed up to the uterine fundus, but the bilateral tubal ostia could not be identified due to extensive scarring.

Despite these efforts, the bilateral tubal ostia remained obscured by the extensive fibrosis. To prevent re-adhesion of the uterine walls, a poloxamer-chitosan gel was applied as a barrier. One month post-procedure, cyclical estrogen-progesterone therapy was prescribed, resulting in a 3-day menstrual period.

## DISCUSSION

Genital TB mainly affects individuals of reproductive age, between 20 and 45 years old<sup>5</sup>. Genital TB can extend to the endometrium in about 50% of cases, where it persists in the basal layer. This layer is not shed during menstruation and may contribute to re-infection. The tuberculous uterus triggers a chronic inflammatory response and forms epithelioid granulomas, which are the hallmark of TB infections. Further inflammation can lead to endometrial ulcers, fibrosis, and scarring, ultimately resulting in partial or complete intrauterine adhesions, obliteration, and deformity of the uterus<sup>6</sup>.

In this case, the patient was diagnosed with unexplained primary amenorrhea after ruling out common underlying causes of amenorrhea, such as outflow tract abnormalities, ovarian insufficiency, hypothalamic or pituitary disorders, endocrine gland disorders, and physiological or medication-induced factors<sup>7</sup>. Pulmonary TB has been found to cause hypothalamic-pituitary dysfunction, premature ovarian failure, or organic lesions in the uterine endometrium, leading to hypomenorrhea or secondary amenorrhea<sup>8</sup>. Although menstrual cessation or reduced menstrual bleeding flow and duration have been reported in pulmonary TB patients, primary amenorrhea in TB patients is rare. The failure to induce menstruation despite hormonal combination treatment to stimulate the endometrium, along with confirmed normal hypothalamic-pituitary-ovarian function, suggests uterine synechiae as the cause of amenorrhea<sup>9</sup>.

Patients with clinical manifestations and a history of TB infection or exposure should be suspected of having genital TB, where the disease has been reported to cause approximately 4% of uterine synechiae cases<sup>10</sup>. Uterine synechiae can be underdiagnosed, as they are often undetectable by routine examinations or diagnostic procedures, such as ultrasound. Radiologic evaluation may provide clues to *M. tuberculosis* in the endometrium. Evaluation of the endometrium with transvaginal ultrasonography can show endometrial thickening

or pyometra, while a hysterosalpingogram can show uterine distortion. The diagnosis of endometrial TB can be confirmed through granulomatous histopathology from biopsy or tissue curettage<sup>11</sup>. In addition, an endometrial biopsy can be used for acid-fast bacilli staining and mycobacterial culture. Menstrual fluid can also be utilized to diagnose TB endometritis<sup>12</sup>. To diagnose the extent of uterine synechiae, hysteroscopy is usually the diagnostic gold standard.

In this case, the endometrial tissue evaluation showed chronic inflammation, but no caseating granulomas were found. Caseating endometrial granulomas are more commonly observed in postmenopausal women compared to those of reproductive age, as the endometrium is typically expelled before caseation develops in reproductive-age women<sup>13</sup>. As such, endometrial biopsies are recommended to be performed during the premenstrual or late secretory phase, when granulomas are more likely to be present and well-developed throughout the menstrual cycle<sup>13,14</sup>.

In our case, the diagnosis of genital TB was confirmed by a positive IGRA result from the patient's peripheral blood sample. In recent years, the IGRA has been used for diagnosing active and latent TB infection<sup>15-17</sup>. In women with confirmed female genital tuberculosis, the sensitivity and specificity of the IGRA test were found to be 86-94% and 70-75%, respectively, compared to the control group<sup>18,19</sup>.

The treatment of genital TB is similar to that of pulmonary TB. According to the Indonesian Ministry of Health (2021), patients with genital TB are treated with a 6-9-month regimen. The treatment regimen includes 2 months of intensive phase therapy with a combination of four drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a 4-7-month continuation phase therapy with isoniazid and rifampicin<sup>11</sup>. After treatment with antituberculosis drugs, the endometrium can revert back to normal, and patients may experience improvement in their menstruation cycles. However, in cases with extensive

endometrial gland damage, the endometrium may not respond to hormonal stimulation, thus preventing or delaying endometrial regeneration. In such cases, endometrial regeneration and the return of menstrual cycles can take years, even with proper treatment<sup>20</sup>. Laparoscopy and hysteroscopy can be repeated after completion of antituberculosis treatment to monitor disease resolution and assess the prognosis for infertility treatment. If major adhesions, frozen pelvis, or blocked fallopian tubes persist with or without signs of diminishing minor lesions after the treatment regimen, the fertility prognosis is poor<sup>21</sup>. Accordingly, in this case, the patient underwent a second-look hysteroscopy procedure after TB treatment completion, followed by administration of cyclical estrogen-progesterone, resulting in a 3-day menstrual period.

## CONCLUSIONS

Tuberculous endometritis is a type of extrapulmonary tuberculosis that affects women. Diagnosing tuberculous endometritis is challenging due to its nonspecific signs and symptoms. In this case, we present the rare occurrence of tuberculosis-related uterine synechiae leading to primary amenorrhea, highlighting the importance of considering tuberculosis in the differential diagnosis of unexplained primary amenorrhea, especially in TB-endemic regions.

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