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Endometrial Tuberculosis and Secondary Amenorrhea: A Report of Three Cases in Sudan

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ABSTRACT

Background: Female genital tuberculosis is an important cause of secondary amenorrhea and infertility in developing countries where tuberculosis is endemic.
Objectives: We present three cases in which endometrial tuberculosis was a cause of secondary amenorrhea and infertility.
Patients and Methods: In a retrospective study from January 2007 to June 2010, we conducted 1010 laparoscopies for infertile patients. Among these patients, three had secondary amenorrhea and infertility; therefore, they underwent hysteroscopy and endometrial biopsy.
Results: The laparoscopic findings showed normal uterus and ovaries in all three patients; although the fallopian tubes were patent in one patient, they blocked in the other two. Hysteroscopy findings revealed that the endometrial layer was atrophied in all three patients, and biopsy results revealed the presence of acid-fast bacilli using Zeihl-Neelsen stain.
Conclusions: Patients with genital tuberculosis may have no documented history of tuberculosis or may have evidence of tuberculosis lesions elsewhere in the body. Histopathological evidence from biopsies of premenstrual endometrial tissue or demonstration of tubercle bacilli in cultures of menstrual blood or endometrial curetting is necessary to reach a conclusive diagnosis of the disease. When our patients were treated with antituberculosis treatment for 1 year they regained their menstruation but did not achieve pregnancy. Of note, if a patient conceives after genital tuberculosis infection, there is an increased chance of an ectopic pregnancy as a consequence of chronic salpingitis and tubal damage. Gynecologists in developing countries must consider genital tuberculosis as an important cause of tubal blockage and secondary amenorrhea that leads to infertility.

Implication for health policy/practice/research/medical education:
The article is useful for the gynecologists in developing countries to consider genital tuberculosis as an important cause of secondary amenorrhea and infertility .

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1. Background

Female genital tuberculosis is an important cause of secondary amenorrhea and infertility in developing countries where tuberculosis is endemic (1). Genital tuberculosis is typically asymptomatic and is usually diag-

nosed incidentally during infertility investigations (2). Symptomatic disease usually presents with infertility, pelvic pain, and/or menstrual irregularities (3). Infertility is typically caused by pathology in the endometrium and fallopian tubes and a blockage of ovum transport, and dysfunction of menstruation is largely attributed to endometrial caseation (4, 5). The antigonadotrophic effect of Mycobacterium tuberculosis may be responsible for the menstrual irregularities that take place in cases of active pulmonary tuberculosis without genital tract lesions (5). Diagnosis of genital tuberculosis is difficult, even when grounds for suspicion exist. In 2007, the World Health Organization (Global Tuberculosis Control) stated that in 92% of cases, diagnosis of genital tuberculosis is secondary to lesions found in the lungs, lymph nodes, urinary tract, bones, or joints (6). The differential diagnosis of female genital tuberculosis includes chronic pelvic inflammation, mycotic infection, enterobiasis, lipid salpingitis, and carcinoma (7). The endometrium is involved in approximately 50–60% of women with genital tuberculosis. Hysteroscopy provides direct information about endometrial trophicity, and may reveal a scarred atrophic endometrial layer with adhesions varying from mild to severe, leading to Asherman's syndrome and secondary amenorrhea (4).

2. Objectives

In this study, we report three cases in which endometrial tuberculosis was a cause of secondary amenorrhea and infertility.

3. Patients and Methods

Patients were referred to the Minimal Access Gynecological Surgery (MAGS) Center at Omdurman Maternity Hospital by gynecologists from the same hospital, other local hospitals, Family Planning Clinics, and the private sector for laparoscopy (in cases of infertility and chronic pelvic pain) and hysteroscopy. Hysteroscopy was performed on patients with amenorrhea or suspected intracavitary lesions such as uterine septa or adhesions. From January 2007 to June 2010, we conducted 1010 laparoscopies on infertile patients. Laparoscopies were performed in the standard manner under general anesthesia. Among these patients, three presented with secondary amenorrhea and infertility; consequently, hysteroscopies were also performed along with endometrial biopsies. The endometrial tissue was studied using Zeihl-Neelsen (ZN) stain for acid-fast bacilli (AFB). Patient follow-ups were conducted at six months and one year after the surgery.

4. Results

4.1. Case 1

A 35-year-old housewife, para II, was referred to our clinic with a two-year history of infertility and amenorrhea. She denied any fever, cough, or chest pain. The general physical examination was normal with no palpable lymph nodes, and the systemic examination did not reveal any abnormality. The patient was referred to our center for further investigations regarding her condition. In routine laboratory examinations, her erythrocyte sedimentation rate (ESR) was found to be elevated (ESR 100 after 1 hour). The results of other biochemical tests were in the normal range, and the hormonal profile was also normal. Laparoscopic surgery was performed and revealed normal uterus and ovaries, patent fallopian tubes, and no pelvic adhesions. To further aid in the investigation and diagnosis, a hysteroscopy was performed. that detected an adhesion band at the level of the cervical canal, a small uterine cavity, and an atrophic endometrium with an adhesion. These adhesion bands were divided, a Nova T IUCD was inserted, and an endometrial biopsy was taken and sent for histopathological examinations. The biopsy revealed the presence of AFB by ZN staining. Hormonal and anti-tuberculosis therapy (four drugs: isoniazid, ethambutol, rifampicin, and pyrazinamide) were administered.

4.2. Case 2

A 30-year-old woman, para IV, and married for 16 years was referred to our clinic with a 2-year history of secondary amenorrhea. She had not experienced any other significant medical or surgical illnesses in the past. Her systemic examinations were normal. Her routine laboratory investigations showed an increased ESR (80 for 1st hour); however, other biochemical tests were normal. Laparoscopic and hysteroscopic examinations were performed. The laparoscopic examination revealed normal uterus and ovaries. However, both fallopian tubes were blocked and pelvic adhesions were present. The hysteroscopy showed a small uterine cavity, and an atrophic endometrium with no adhesions. An endometrial biopsy was taken and sent for histopathological examinations.. The histopathological results revealed presence of AFB. The patient subsequently received antituberculosis treatment (four drugs: isoniazid, ethambutol, rifampicin, and pyrazinamide).

4.3. Case 3

A 28-year-old housewife presented with a 12-year history of infertility and 2 years of secondary amenorrhea. Her past medical history was unremarkable and her systemic examinations were normal. Routine laboratory investigations showed an elevated ESR (65 for 1st hour); however, other biochemical investigations and her hormonal profile were within the normal range. Laparoscopy and hysteroscopy procedures were performed. The laparoscopic examination showed a normal uterus, blocked fallopian tubes, normal ovaries, and no pelvic adhesions. The hysteroscopy revealed a small uterine cavity and an atrophic endometrium with no adhesions (*Figure 1*). An

endometrial biopsy was taken and sent for ZN staining. The biopsy was positive for AFB. The patient subsequently received antituberculosis therapy (comprising the aforementioned four drugs).

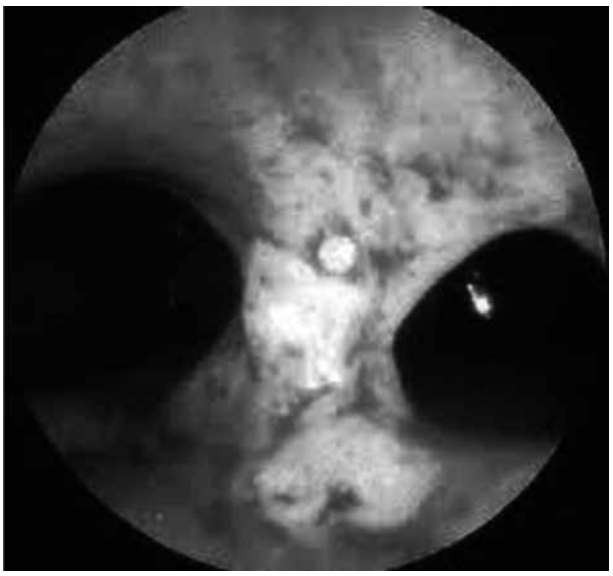

Figure 1. Hysteroscopy Image Showing Cavity Abnormalities—As a Consequence of Genital Tuberculosis

4.4. Patient Follow-ups

In all three patients, follow-ups were conducted at six months and one year; all had started menstruation at six months, albeit irregularly. At one year, the menses were regular, and menstrual blood loss had increased in amount; however, there were no pregnancies.

5. Discussion

Patients with genital tuberculosis may have no documented history of tuberculosis or may have evidence of tubercular lesions elsewhere in the body. Abdominal and vaginal examinations may be normal. A high erythrocyte sedimentation rate and a positive Mantoux test are nonspecific, and therefore cannot provide an accurate diagnosis of genital tuberculosis. Chest X-rays are normal in most cases; however, pelvic ultrasound and hysterosalpingography examinations may aid in the diagnosis. Histopathological evidence from biopsies of premenstrual endometrial tissue or the demonstration of tubercle bacilli in cultures of menstrual blood or endometrial curetting is necessary to provide a conclusive diagnosis of the disease (3, 7, 8). In our study, pulmonary lesions were not seen in the reported cases. All three patients denied contact with active tuberculosis. Chest X-ray was not performed for these patients, as there were no symptoms to indicate its necessity. ZN staining of AFB requires a large number of bacteria (a minimum of 10^5/ml) to be present in the specimen (9). In our cases, both histopathological and microbiological studies showed positive ZN staining for AFB, and this was our main diagnostic method that confirmed our clinical diagnosis. Newer techniques, such as polymerase chain reaction (PCR), can detect genital tuberculosis from clinical samples earlier and are less invasive (10). However, most of these techniques are too expensive and complicated to be of any practical benefit to the vast majority of tuberculosis patients living in developing countries.

It has been estimated that 5–10% of infertile cases are a result of female genital tuberculosis and even this rate is higher among patients with tubal factor infertility (39- 41%) (8). The most common genital organs involved are fallopian tubes (95-100%), endometrium (50–60%), and ovaries (20–30%) (2, 3, 11) respectively. Two out of our three patients presented with fallopian tube blockage, and one had a pelvic adhesion. This is in agreement with the study conducted by Jahromi *et al.* (4), in which the laparoscopies conducted on infertile patients revealed tubal involvement in 60% of patients and a frozen pelvis in 17.2%. Each of the patients in our three cases was treated with combined antituberculosis drug therapy for 9–12 months with close monitoring for any adverse effects of the drugs or evidence of microbial resistance. This is the same treatment protocol used in patients with pulmonary and extrapulmonary tuberculosis (1, 3, 6). In Sudan, there have been reports of multi-drug resistant tuberculosis (6); however, in our cases, the culture and sensitivity test for M. tuberculosis was not performed. Fortunately, all of our reported patients were successfully treated; they all regained their menstruation, although did not achieve pregnancy. It is important to note that if after treatment a patient conceives, there is an increased chance of an ectopic pregnancy as a consequence of chronic salpingitis and tubal damage. If pregnancy progresses, pre-term labour and abnormal placentation are possible complications. Importantly, timely therapy at an early stage of genital tuberculosis typically completely resolves the disease, resulting in successful pregnancy (12). In vitro fertilization with embryo transfer remains the most effective method of treatment associated with infertility (11-13).

There is a strong association between genital tuberculosis and secondary amenorrhea; therefore, genital tuberculosis would be more frequently diagnosed if this possibility was considered in the evaluation of every patient presenting with secondary amenorrhea in areas where tuberculosis is endemic (14, 15). Tuberculosis is a chronic infectious disease in Sudan (16). Genital tract tuberculosis has been recognized and treated for more than two centuries, although the actual incidence of pelvic tuberculosis in Sudan is still unknown. We believe that the incidence of pelvic tuberculosis in Sudan is possibly as high as other sub-Saharan African countries; therefore, clinicians in Sudan as well as developing countries must consider genital tuberculosis as an important cause of tubal blockage and secondary amenorrhea that leads to infertility

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Authors' Contribution

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