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Hard to Conceive

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Abstract

In this *Journal* feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

A 31-year-old woman reported to her primary care physician that she and her husband had been unable to conceive a child since abstaining from all contraception 18 months earlier. The patient's menarche occurred when she was 13 years old, and her menses recurred reliably every 4 weeks, lasting for 6 to 7 days. She had no history of sexually transmitted disease, pelvic inflammatory disease, use of an intrauterine device, exposure to diethylstilbestrol, an abnormal Papanicolaou (Pap) smear, or pregnancy.

One year before presentation, she had been evaluated by her physician for abdominal pain in the left lower quadrant, with no fevers, chills, or weight loss. Pelvic and transvaginal ultrasonography performed at that time showed a normal uterus and ovaries. Cervical genetic probes for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were negative. The pain resolved spontaneously and did not recur.

The patient presents with infertility, which is defined as the inability to conceive after 1 year of regular unprotected intercourse. Within the first year of attempted conception, 80 to 90% of couples conceive, and after 2 years 95% conceive. Three quarters of infertility cases have an identifiable cause; the rest are designated as "unexplained." The majority of cases of female infertility result from disorders of ovulation or the fallopian tubes; other causes include endometriosis, cervical defects, and uterine abnormalities. The predominant cause of male infertility is a low number of functional sperm in the ejaculate.

The patient reports no known history of pelvic inflammatory disease or sexually transmitted disease that would explain tubal infertility, but her history of unilateral lower abdominal pain could be indicative of prior occult tubal infection, endometriosis, or pelvic adhesions; pelvic ultrasonography is insensitive for the detection of these conditions. She does not have irregular menses, which is common in ovulatory dysfunction. The focus of further questions about her medical history and of the physical examination should be an assessment for symptoms and signs of androgen excess (e.g., hirsutism or acne), thyroid dysfunction, and abnormalities in the genital and pelvic organs. Her partner should also be evaluated, with attention to any history of systemic illness, medications, or localized trauma that could cause

gonadal dysfunction; this would include a history of mumps, testicular trauma, chemotherapy, or exposure to environmental toxins (e.g., lead or mercury).

The patient's medical and surgical history were unremarkable, and she reported no constitutional or focal symptoms. She was taking prenatal vitamins but no medications. She has no allergies. She reported having received bacille Calmette–Guérin (BCG) vaccination against tuberculosis as an infant. She was born and raised in Kathmandu, Nepal, and had moved to the United States 4 years earlier with her husband, who was pursuing an employment opportunity. As part of the immigration process, she underwent screening for latent tuberculosis infection and received a “borderline positive” result on a tuberculin skin test with a purified protein derivative. She was told that this result was due to her BCG vaccination and did not receive treatment for latent tuberculosis infection. She was vaccinated for measles, mumps, and rubella. She had never been tested for infection with the human immunodeficiency virus (HIV). As a child, she had consumed buffalo's milk and cow's milk and could not confirm their pasteurization. She did not smoke, drink alcohol, or use recreational drugs. She worked as an accountant.

The determination of a positive finding on a tuberculin skin test depends on the size of skin induration, whether the person being tested is immunocompromised, and whether there is a history of known exposure to a person with active tuberculosis or a high likelihood of exposure (e.g., because the person is a health care worker or prisoner or is homeless). Although this patient has no medical impairments or known contacts with persons with tuberculosis, she is a recent emigrant (having moved within the past 5 years) from a country with a high prevalence of tuberculosis. In such a case, an induration measuring 10 mm or more in diameter would be interpreted as a positive test result, but the information on the results of her test is insufficient to make a determination; exposure to tuberculosis should be assumed until proved otherwise. She has no cough or constitutional symptoms that would suggest active tuberculosis.

The patient's husband was 35 years old and reported that he had not fathered any children. He had no notable medical history and took no medications. He did not smoke, consumed one alcoholic beverage per week, and reported no use of recreational drugs. There was no family history of cystic fibrosis or developmental disorders. The results of HIV and tuberculin skin tests performed at the time of his emigration from Nepal were negative.

On physical examination, the patient appeared to be well. Her weight was 55 kg, body-mass index (the weight in kilograms divided by the square of the height in meters) 22.3, temperature 36.7°C, blood pressure 104/74 mm Hg, pulse 95 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 100% while she was breathing ambient air. There was no adenopathy or thyromegaly, and there were no thyroid nodules. There was no galactorrhea. The results of respiratory, cardiac, and musculoskeletal examinations were normal. There was no abdominal tenderness or hepatosplenomegaly. External genital examination showed a normal-appearing clitoris and labia. Bimanual pelvic examination revealed no adnexal or uterine masses or tenderness. Speculum examination of the vaginal vault and cervix revealed no discharge or ulceration, and there was no cervical motion tenderness. Skin examination showed no facial acne, coarse terminal hair, male-pattern baldness, or hyperpigmentation of the axillae or intertriginous areas.

Levels of serum electrolytes, blood urea nitrogen, and creatinine were normal, as were the results of liver-function tests. The white-cell count was 10,180 per milliliter, with 72% polymorpho-nuclear cells, 22% lymphocytes, 5% monocytes, and 1% eosinophils. The hematocrit was 36%, and the platelet count 308,000 cells per milliliter. Cervical cytologic

examination showed no abnormalities. Repeat genetic probes for *C. trachomatis* and *N. gonorrhoeae* were negative.

The patient and her husband have no apparent current or past medical conditions that explain their infertility. Given the duration of their inability to conceive, referral to a fertility specialist is warranted. The initial diagnostic evaluation should include semen analysis, documentation of ovulation, and hysterosalpingography to evaluate the uterine cavity and tubal patency.

The couple was seen by an obstetrical–gynecologic fertility specialist. The husband's semen analysis showed a semen volume of 1.7 ml (normal range, 2). The sperm concentration was 113 million per milliliter (normal range, 20 million), and morphologic characteristics were normal in 31% of sperm (normal range, >14%), with no defects in the head or tail. Sperm motility, which was evaluated manually at room temperature, was normal. The patient's level of follicle-stimulating hormone on cycle day 3 was normal, at 5.9 mU per milliliter (normal range, 3.9 to 13.2), as were levels of luteinizing hormone (5.0 mU per milliliter; normal range, 2.4 to 12.6) and estradiol (52 pg per milliliter [201 pmol per liter]; normal range, 14 to 188 [51 to 690]). The level of midluteal progesterone was 3.3 ng per milliliter (10.5 nmol per liter; normal postovulatory range, 1.7 to 27.1 [5.4 to 86.2]). A hysterosalpingogram revealed a normal uterus and endometrial cavity without synechiae. Both fallopian tubes filled with contrast medium and were of normal caliber. However, there was no distal spill of contrast medium from either fallopian tube (Fig. 1).

The patient's normal menstrual history and progesterone level (according to the assay used) make anovulation an unlikely cause of her infertility. The semen analysis is central to the evaluation of male infertility. The husband's semen volume was somewhat low, but sperm morphologic characteristics, concentration, and motility were normal, making male-factor infertility unlikely. Findings on hysterosalpingography suggest that the infertility is most likely related to bilateral distal tubal obstruction. Distal tubal blockage most commonly results from pelvic inflammatory disease and salpingitis; the most common causes include infection with *C. trachomatis* or *N. gonorrhoeae*, but blockage can also result from mixed infection with mycoplasma, ureaplasma, obligate anaerobes, and coliform species and from mycobacterial infections — notably, *Mycobacterium tuberculosis*. Pelvic adhesions, endometriosis with tubal implantations, and bacterial peritonitis can also cause tubal scarring and obstruction. In this case, the bilateral distal blockage of the fallopian tubes requires treatment with in vitro fertilization (IVF) or tubal surgery.

IVF treatment was started with low-dose luteal leuprolide acetate to prevent an endogenous surge of luteinizing hormone that could cause premature luteinization of follicles or premature ovulation of oocytes before retrieval. Injections with follicle-stimulating hormone were used to stimulate multifollicular development. The patient had an excellent estradiol response, and 21 oocytes were retrieved; two embryos were transferred into the uterus but did not result in a pregnancy. A subsequent IVF cycle with the use of two frozen embryos also failed to result in a pregnancy.

Endometrial biopsy is not warranted in the routine evaluation of infertility, but it should be considered early in the diagnostic workup of a patient from a region in which tuberculosis is endemic. The finding of distal tubal occlusion also argues for endometrial biopsy to assess for the presence of endometritis.

After the two unsuccessful cycles of IVF, an endometrial biopsy was performed. The specimen showed several non-necrotizing granulomas (Fig. 2).

With rare exceptions, granulomatous endometritis suggests an infection, such as brucellosis, fungal infection, or mycobacterial endometritis; most cases of mycobacterial endometritis are caused by *M. tuberculosis* complex — either *M. tuberculosis* or *M. bovis*. Ingestion of unpasteurized milk places the patient at risk for infection with *M. bovis* and brucella species. Resistance to pyrazinamide on antimicrobial susceptibility testing of *M. tuberculosis* complex may signal infection with *M. bovis*. Cases of disseminated *M. bovis* infection from BCG vaccination are rare, but when they do occur, they are most likely to appear in children and patients with compromised immune systems. Disseminated fungal infection with cryptococcus, coccidioides, blastomyces, or histoplasma species can cause granulomatous endometritis, but this condition would be unusual in an immunocompetent patient. Parasitic causes (e.g., cyclospora and cryptospora) are rare. This patient does not have a history that suggests noninfectious causes of uterine granuloma, which include reaction to an intra-uterine device or another foreign body, vasculitis, sarcoidosis, and radiation therapy. Given her upbringing in Nepal and the findings on microscopy, genital tuberculosis is of primary concern.

Because of the previous nondiagnostic tuberculin skin test and the patient's history of BCG vaccination, tuberculin skin testing was not repeated. Instead, an interferon-gamma release assay of a whole-blood sample was used as an assessment for exposure to *M. tuberculosis*, and the result was positive. A chest radiograph showed no cavitation, infiltrate, scarring, or effusion. A second endometrial biopsy was performed to allow for further microbiologic and pathological analysis, which revealed non-necrotizing granulomas, with visualization of a single acid-fast organism (Fig. 3).

Therapy with isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine was started. Within 6 weeks, cultures became positive for *M. tuberculosis* complex that was resistant only to isoniazid and streptomycin. Isoniazid was discontinued, and the patient completed a 6-month course of ethambutol, pyrazinamide, and rifampin without complications. Pathological examination of tissue from a repeat endometrial biopsy performed after treatment revealed no granulomas or acid-fast organisms. The patient has undergone one subsequent cycle of IVF but did not become pregnant.

COMMENTARY

In the United States, approximately 10% of women of reproductive age have received infertility treatment. The prevalence of infertility in developing countries is probably greater than 10%.¹ Among cases of infertility, about 50% are attributed to female factors, and 25% to male factors; 25% are unexplained.² The percentage of cases considered to be unexplained would be lower if laparoscopy were routinely included in the evaluation, since this procedure can be used to diagnose conditions that might otherwise go unrecognized, such as endometriosis and, as in the present case, tuberculosis.

Although genital tuberculosis is rarely the cause of infertility in areas where there is a low prevalence of tuberculosis,³ it should be considered routinely as a potential cause of infertility in areas where the infection is endemic. The estimated prevalence of genital tuberculosis varies widely — from 2 to 25% — among infertile women in developing countries, depending on the geographic location and the case definition used.^{4,5}

Genital tuberculosis typically arises from hematogenous dissemination of a primary pulmonary inoculum to the fallopian tubes in women (causing salpingitis) and to the epididymis and testes in men (causing prostatitis, urethritis, and epididymitis). However, cases of tuberculous salpingitis resulting from local spread of enteritis or peritonitis have been reported.⁶ Endometritis, cervicitis, and peritonitis occur by means of local extension from salpingitis or through hematogenous spread. Reactivation of genital tuberculosis occurs

in two phases: an initial exudative phase, with ulceration of the fallopian-tube wall, and a secondary adhesive phase, during which large tubercles form thick perisalpingeal adhesions, leading to tubal obstruction.⁷

As in this patient, the clinical presentation of genital tuberculosis is often subtle, and at least 10% of patients have no apparent manifestations of disease. The major symptoms and signs of genital tuberculosis in women are infertility, pelvic pain, and menstrual irregularities, including postmenopausal bleeding.⁸ Constitutional manifestations of disseminated tuberculosis, such as fever, weight loss, and night sweats, rarely occur in patients with isolated genital tuberculosis.⁶

The most common radiographic findings in cases of tuberculous salpingitis are scarring and blockage of the fallopian tubes, which have a “pipe stem” or “beaded” appearance; calcium in the pelvis; a distorted endometrial contour; and hydrosalpinx. However, these findings are not sufficiently specific to establish the diagnosis.⁹ Endometrial biopsy can provide a definitive diagnosis; alternative sources of samples for acid-fast staining and culture include menstrual fluid and ascites. However, the low sensitivity of endometrial mycobacterial culture and microscopy (40% and 60%, respectively, in small studies) limits the usefulness of these tests in detecting tuberculosis.³ A mycobacterial polymerase-chain-reaction assay of endometrial fluid or tissue can serve as a rapid adjunctive diagnostic tool.¹⁰ In the absence of a definitive microbiologic study, the presence of a necrotizing granuloma strongly suggests a diagnosis of tuberculosis if there is no alternative explanation.

False positive reactions to a tuberculin skin test may occur after BCG vaccination or infection with nontuberculous mycobacteria. In persons from regions where tuberculosis is endemic, however, a positive skin test (as assessed on the basis of the size of the skin induration, immune status, and status with respect to the risk of exposure) should be considered to indicate a high likelihood of previous tuberculosis, especially if the vaccination was administered many years earlier, as was true in this patient. False negative results can occur in patients who are immunocompromised and in those who have severe malnutrition or active tuberculous infection or who have had subcutaneous rather than intradermal administration of a tuberculin skin test.

Interferon-gamma release assays of whole blood, such as the QuantiFERON–TB Gold (QFT) test (Cellestis) and the T-SPOT.TB test (Oxford Immunotec), quantify the release of interferon gamma by mononuclear cells exposed to *M. tuberculosis* antigens. Because the genes that encode these antigens (early secretory antigenic target 6 [ESAT-6] and culture filtrate protein 10 [CFP-10]) are absent in most mycobacteria other than *M. tuberculosis*, including *M. bovis* (used in the BCG vaccine), these tests are highly specific for *M. tuberculosis* and may be particularly useful in the assessment of patients who have had BCG vaccination. In a meta-analysis of the performance of these tests, the pooled average specificity for the detection of latent tuberculous infection was 97% with the QFT test and 92% with the T-SPOT.TB test.¹¹ An additional advantage of these assays is that they require only a single visit; tuberculin skin testing requires a second visit for evaluation of skin induration. The Centers for Disease Control and Prevention supports the use of the interferon-gamma release assay as a screening tool for tuberculosis exposure for all circumstances in which tuberculin skin testing has been used and is preferred for testing of patients who have had BCG vaccination or are unlikely to return for test interpretation. Further study is required to determine the role of these assays in evaluating children, immunocompromised patients, and patients with suspected active tuberculosis.¹²

Tubal and endometrial scarring are well-recognized sequelae of genital tuberculous infection, but there is a lack of data from prospective studies assessing the efficacy of

antituberculosis therapy and IVF on fertility in affected patients. In addition to mechanical factors, decreased ovarian reserve may contribute to infertility in women with tuberculosis. However, the mechanism underlying decreased reserve has not been clearly delineated, and the findings come from a single retrospective analysis of women with genital tuberculosis who required higher doses of exogenous gonadotropins to achieve ovarian hyper-stimulation than controls with tubal infertility from other causes.¹³ A case report of congenital tuberculosis in an infant conceived by means of IVF in a woman with undiagnosed genital tuberculosis further underscores the importance of recognizing and treating this disease.¹⁴

A careful history taking, with attention to the patient's country of origin and foreign travel, together with the use of new strategies for the diagnosis of tuberculosis, can facilitate diagnosis of the disease in cases in which it is unexpected. This approach may also help infertile couples conceive.

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Figure 1. Radiograph Obtained during Hysterosalpingography

The absence of intraperitoneal spillage of contrast material, administered with the use of fluoroscopic guidance through the cannulated cervical os, is diagnostic of bilateral blockage (arrows) of the fallopian tubes.

Figure 2. Endometrial-Biopsy Specimen

Staining with hematoxylin and eosin reveals non-necrotizing granulomas (arrows) within the endometrial stroma. Image courtesy of Dr. Rachel Factor, Brigham and Women's Hospital.

Figure 3. Second Endometrial-Biopsy Specimen

Acid-fast staining reveals a single organism (arrow) within the endometrial granuloma. Image courtesy of Dr. Rachel Factor, Brigham and Women's Hospital.