Adverse pregnancy outcomes after in vitro fertilization due to undiagnosed urogenital tuberculosis and proposed screening algorithm for patients from tuberculosis-endemic countries

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Objective: To report 2 cases of adverse pregnancy outcomes due to delayed diagnosis of urogenital tuberculosis and propose a screening algorithm for patients from tuberculosis-endemic countries.
Design: Case report.
Setting: Academic medical center.
Patient(s): Two patients with delayed diagnosis of urogenital tuberculosis leading to a fetal loss and a preterm delivery of an infant with congenital tuberculosis.
Intervention(s): Endometrial biopsy, acid-fast bacilli culture of urine, and endometrium.
Main outcome measure(s): Pregnancy outcomes.
Result(s): Fetal loss at 19 weeks and preterm delivery of an infant with congenital tuberculosis before urogenital tuberculosis treatment.
Conclusion(s): Patients who are at risk of urogenital tuberculosis should be screened in advance of infertility treatment to potentially prevent adverse pregnancy outcomes. (Fertil Steril Rep® 2022;3:285–91. ©2022 by American Society for Reproductive Medicine.)
Key Words: Urogenital tuberculosis, female genital tuberculosis, IVF, congenital tuberculosis, infertility

Urogenital (UG) tuberculosis (TB) accounts for 15%–20% of extrapulmonary TB (1, 2) and is a significant cause of infertility in endemic countries (3). It occurs as an isolated presentation in 5%–30% of cases of urogenital TB (2, 4). The reproductive health implications of TB include infertility from tubal and/or uterine scarring, pregnancy loss, and risk for congenital transmission (1, 3, 5–7). In India, UG TB contributes to half of tubal factor infertility presentations (1). Less common in the United States, the prevalence has been estimated at one percent (8); however, the prevalence may be higher with increased immigration from TB-endemic countries. It is also likely that UG TB is underdiagnosed and underreported in the United States because of its historical rarity, the complexity of

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the infection, and lack of sensitive, definitive diagnostic tests. Delays in diagnosis and treatment confer serious complications, the most devastating of which is late fetal loss or congenital TB transmission (5, 6, 9–12). In the case reports herein, we describe two cases of adverse pregnancy outcomes resulting from UG TB after delayed diagnosis and propose a testing strategy for identifying and screening at-risk individuals based on experience and the current literature.

METHODS

Data collection: We conducted a retrospective chart review of 2 patients and their pregnancy outcomes.

Ethics: All data was obtained from chart review and reported without any patient identifiers. The University of Washington Human Subjects Division (institutional review board) considered this reporting exempt from human subjects research.

RESULTS

Case 1

Patient 1 is a 36-year-old G0 who presented to a local fertility clinic seeking treatment for infertility of 5 years duration. She had immigrated 12 years earlier from Ethiopia. She was ovulatory based on normal menstrual cycles. The patient reported mild dysmenorrhea. Ovarian reserve testing returned antimüllerian hormone level of 1.71 ng/mL, basal follicle-stimulating hormone and estradiol levels were 10.94 mIU/mL and 94.9 pg/mL, respectively, and the antral follicle count on ultrasound was 14. Her husband had a normal semen analysis. Hysterosalpingogram revealed evidence of tubal disease with bilateral proximal tubal occlusion; there was no record if any uterine abnormalities were observed. There was no evidence of hydrosalpinx on ultrasound. During the first cycle of IVF, 3 oocytes were recovered. In a fresh embryo transfer from that cycle, a single euploid blastocyst of good morphologic quality was transferred, and implantation was achieved. Her endometrial lining before the start of progesterone treatment was 11.5 millimeters in thickness and trilaminar in sonographic appearance. Saline infusion sonography or hysteroscopy was not performed before this initial transfer. The patient presented at 19 weeks with advanced cervical dilation, premature and preterm rupture of membranes, and placental abruption resulting in a second-trimester loss at 19 5/7 weeks. A dilatation and curettage were performed to remove the retained placenta. The procedure was complicated by hemorrhage; she did not require additional interventions or transfusion support. Gross pathology of the fetus and placenta was reported as normal, except for a mild cleft palate. After the loss and procedure, she experienced an onset of hypomenorrhea, with both fewer frequency of cycles and lighter flow. The saline infusion sonography procedure performed in evaluation revealed a normal cavity without adhesions. She underwent 2 additional in vitro fertilization (IVF) cycles at the clinic. One utilized preimplantation genetic testing aneuploidy (PGT-A) of embryos. Seven oocytes were retrieved, and resulted in one euploid embryo and one mosaic embryo of good morphologic quality. Neither resulted in implantation after a single embryo transfer in a controlled endometrial preparation frozen-thawed embryo transfer. Her third cycle at the clinic involved a fresh transfer of 2 non-tested good, quality blastocysts; no supranumerary embryos were available for cryopreservation. All of the patient's 3 transfers after her pregnancy loss were noted to be easy; one, however, was complicated by retained embryo because of a blood clot at the tip of the catheter. The endometrial lining in advance of each transfer was measured to be 8 mm or greater in thickness and trilaminar in sonographic appearance.

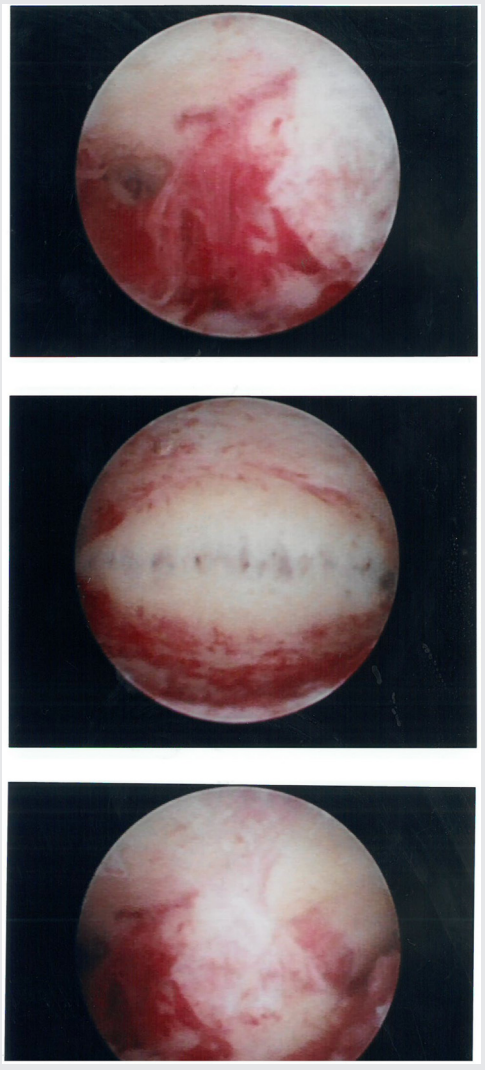
Soon after, she subsequently presented to another regional fertility clinic. A hysteroscopy was performed to evaluate her cavity in a setting of implantation failure and suspected Asherman syndrome in the setting of the risk factor of second-trimester loss surgical management. Operative findings were notable for a pale-appearing endometrium and loose, polypoid tissue (Figure 1). Some mild adhesions were noted at the fundus. Foci of loose, polypoid tissue were excised and sent for pathology, which revealed nonnecrotizing granulomas and a few acid-fast bacilli consistent with TB (Figure 2), prompting consultation with an infectious disease specialist. An interferon-gamma release assay (IGRA) QuantiFERON, was performed after pathology results were positive.

The patient had a history of reactive purified protein derivative, also known as a TST (tuberculin skin test), which had been previously attributed to her having received the Bacillus Calmette-Geurin (BCG) vaccine as a child. She lacked symptoms concerning active pulmonary TB, such as cough, weight loss, fever, or night sweats. The patient had 3 prior normal plain chest radiographs (CXRs). She completed all necessary screening for immigration purposes, and the UG TB went undetected.

To obtain sensitivities, an infectious disease specialist recommended an endometrial biopsy be sent for culture. The subsequent culture was positive for *Mycobacterium tuberculosis* (MTB) which was sensitive to all first-line agents. *Mycobacterium tuberculosis* urine polymerase chain reaction (PCR) and culture were also positive at the time of evaluation by the ID specialist. During her ID evaluation, a CXR was normal and did not show any evidence of pulmonary disease. She then underwent 6 months of standard multidrug therapy: 2 months of rifampin (RIF), isoniazid (INH), pyrazinamide, and ethambutol (RIPE), followed by 4 months of INH and RIF for chronic UG TB.

After completion of the treatment, she had a second hysteroscopy during which additional sparse intrauterine adhesions were excised. After the second surgery, her menstrual bleeding pattern and flow improved; however, her endometrial lining remained thin. She began a series of mock endometrial preparation protocols, including natural cycle, oral estrogen (Estrace), estrogen patches, and addition of vaginal sildenafil to optimize endometrial development. The endometrial thickness did not exceed 5 millimeters and a small amount of fluid remained present throughout the length of the cavity. Subsequently, a gestational carrier was recommended by her clinician based on the abnormal endometrial development and a lack of confidence in the ability of her uterus to sustain a pregnancy to viability.

FIGURE 1



Hysteroscopy (Case 1) notable for a pale-appearing endometrium and loose, polypoid tissue.

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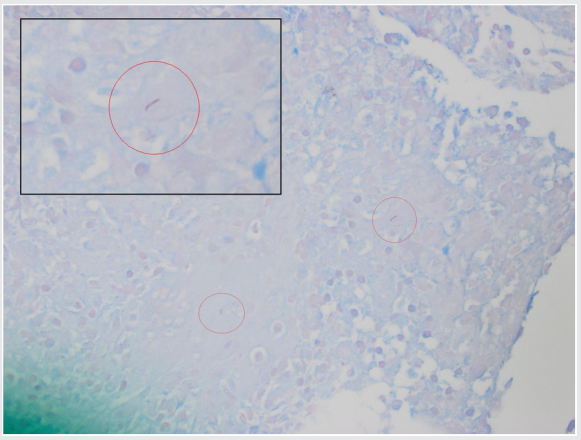
Case 2

Patient 2 is a 30-year-old G0 female with a history of tubal factor infertility who became pregnant after IVF performed at a fertility center in India just before moving to the United States. Records were not available for her infertility evaluation and treatment from India. The pregnancy course was complicated by preterm labor, for which she received intravenous magnesium and 2 doses of betamethasone prior to delivery.

A male infant was born at 30 5/7 weeks (1680 g) by vaginal delivery. He required continuous positive airway pressure for oxygen desaturations after birth but was weaned to room air shortly thereafter. However, on DOL 27, he began having apneic events and fluctuating hypoxia, which intermittently required high flow oxygen via nasal cannula. He was also given an empiric course of broad-spectrum

FIGURE 2



Endometrial biopsy histopathology with AFB stain showing acid-fast bacilli, MTB (red circles) within granulomatous tissue.

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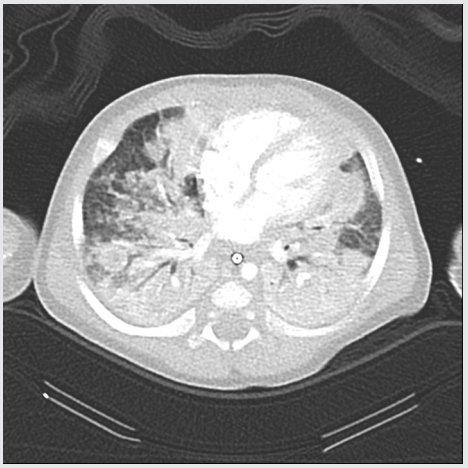
antibiotics. Blood cultures remained negative. On DOL 53 he presented increased respiratory events, including desaturations, retractions, head bobbing, and dry cough. He was restarted on positive pressure ventilation and empiric antibiotics. Chest radiographs revealed increased patchy opacities bilaterally thought initially to be consistent with an atypical or aspiration pneumonia. Blood cultures and respiratory viral panel PCR testing were negative. He remained afebrile, but respiratory symptoms persisted. A chest CT conducted on DOL 60 revealed multiple round pulmonary nodules throughout both lungs (Figure 3). Subsequent bronchoalveolar lavage demonstrated inflammation and turbid fluid, which was Acid-fast bacillus (AFB) smear

FIGURE 3



Chest computed tomography (Case 2 infant at DOL 60) revealing multiple round pulmonary nodules throughout both lungs. Subsequent bronchoalveolar lavage AFB smear positive with culture growing *Mycobacterium tuberculosis (MTB)*.

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positive and later yielded fully-sensitive MTB in culture. Abdominal ultrasound of the infant revealed multiple small hypoechoic lesions in the spleen and kidney consistent with tuberculomas (DOL 60). The infant was initially started on RIF, INH, pyrazinamide, and amikacin until TB meningitis was ruled out. Amikacin was then replaced with ethambutol, and he then continued standard four-drug therapy (RIPE) for the remainder of the 2-month initial phase and then narrowed to INH and RIF for the continuation phase to complete a total 9-month course. He was weaned back to room air 10 days after beginning TB treatment and was discharged home from the neonatal intensive care unit shortly thereafter. Other than minor issues related to prematurity, he continued to recover as an outpatient. He was last seen at 8 months of age and was developing well at that time.

Of note, the maternal gross placenta pathology from the delivery was reported as normal; however, a dilation and curettage procedure 4 days after delivery for endometritis and retained placenta later revealed necrotizing granulomatous inflammation on histopathologic examination. Acid-fast bacillus stain was negative. The entire biopsy specimen was inadvertently placed in formalin before submitting a portion for mycobacteriology; therefore, placental AFB culture was non-diagnostic. The pediatric team was not aware of the placental pathology diagnosis until after the infant's bronchoalveolar lavage revealed AFB because of a communication lapse across institutions with the outside pathologists.

The mother reported no respiratory symptoms, abdominal or pelvic pain, weight loss, fevers, or night sweats before or after the delivery of the infant. On subsequent review of her history, she reported a childhood history of TB treated with multiple drugs for several months; records were not available for her prior remote TB treatment course. Given her history of prior TB and her newborn's diagnosis of congenital TB, a repeat endometrial biopsy was performed in an attempt to confirm the diagnosis of the mother's UG TB. The histopathology again demonstrated granulomatous inflammation with no AFB on the stain. However, again the specimen at that clinic was placed in formalin before submission for AFB culture. The TB PCR test was negative on the fixed tissue block, but the sensitivity of TB PCR on extrapulmonary specimens is limited (13), and non-formalin fixed specimens are preferred for PCR testing despite a lack of definitive data regarding superior sensitivity. An IGRA (QuantiFERON-TB Gold Plus) was positive, and a new CXR was normal. An induced sputum specimen was TB PCR-negative and AFB smear- and culture-negative. She was started on standard anti-TB therapy and completed a six-month course (2 months of RIPE and 4 months of INH and RIF) without regimen-altering adverse effects. Her regimen composition was guided by the drug susceptibility testing results from her newborn's fully-sensitive MTB isolate.

DISCUSSION

Urogenital TB is an important cause of tubal factor infertility in moderate and high-burden countries (1, 3, 7). The diagnosis is not commonly seen in the United States, where the lack of diagnosis can lead, as illustrated in the above case reports, to adverse and severe outcomes of pregnancy, including fetal loss and congenital TB. At our institution, after several decades of negligible occurrence of congenital TB in the United States, we are seeing increasing sporadic cases, with IVF being a common (if not nearly universal) factor in the course of events leading to these cases (5, 6, 11, 12). This is likely a result of the growing populations from TB-endemic settings and increased access to IVF.

In addition to the risks of fetal loss, tubal factor infertility, and congenital TB mentioned above, UG TB can be associated with chronic pelvic pain, pelvic mass, and the formation of sinus tracts necessitating surgical hysterectomy, even after TB treatment has been completed (14). Involvement of the urinary tract can lead to renal scarring, ureteral strictures, urinary outflow tract obstruction, hydroureter, hydronephrosis, renal failure, and reduced bladder capacity. Early diagnosis and treatment are key to preventing these complications (7).

The endometrium is affected in 70% of patients with UG tuberculosis (14). The cavity will appear pale in early infection, often with the presence of small caseous nodes (3, 14). The damage to the endometrium can result in intrauterine synechiae of varying severity, resulting in Asherman syndrome and menstrual abnormalities (3). In addition, the ovarian reserve may be impaired, potentially as a direct impact of infection or chronic inflammation (15). The fallopian tubes can be variably impacted depending on the course of infection but can present with nodular salpingitis and fusion of fimbriae (3). Pelvic adhesions can be of varying grades, both filmy and thick, with tubercles and caseous nodules sometimes visible on laparoscopy (3).

Clinicians providing infertility services to women from countries with high TB burdens, such as India, China, and other Asian and African countries, should consider TB as a potential cause of infertility or pregnancy loss in the appropriate clinical setting, such as tubal disease, uterine factor, or decreased ovarian reserve (16). The challenges of the diagnosis of UG TB include its low incidence, variable clinical presentation, limited sensitivity of diagnostic tests, and lack of standard protocols for triaging and diagnosis of patients. People immigrating to the United States from TB-endemic regions of the world frequently do not report definitive exposure to TB by history; however, it is likely that a substantial proportion of these patients have unknowingly been exposed to TB. Many patients with significant disease progression from UG TB require IVF for conception. Proceeding to IVF without previously completing diagnosis and treatment for potential UG TB will result in lower outcomes, higher rates of pregnancy loss, and the possibility of congenital transmission.

Risk factors for UG TB include patients who have lived in TB-endemic countries and/or have a history of TB diagnosis. We propose that patients who present with unexplained tubal disease and/or uterine synechiae in a setting of one or both the risk factors mentioned earlier should be evaluated for UG TB (Figure 4). A full list of the highest-burden of TB-endemic countries within Africa, Asia, and South America can be found on a website curated by the World Health Organization (16). The list includes but is not limited to China,

TABLE 1

Sensitivity and specificity of latent tuberculosis testing in active tuberculosis (17).

	Sensitivity (range) %	Specificity (range) %	Approximate Cost (US dollar)
QuantiFERON (IGRA)	81 (56–93)	99 (99–100)	90–160
T-SPOT (IGRA)	90 (50–100)	95 (85–100)	45–55
TST (Using >10 mm as size cut off, including BCG vaccinated individuals)	73 (63–82)	66 (34–100)	10–65

IGRA = interferon-gamma release assay; TST = tuberculin skin test.

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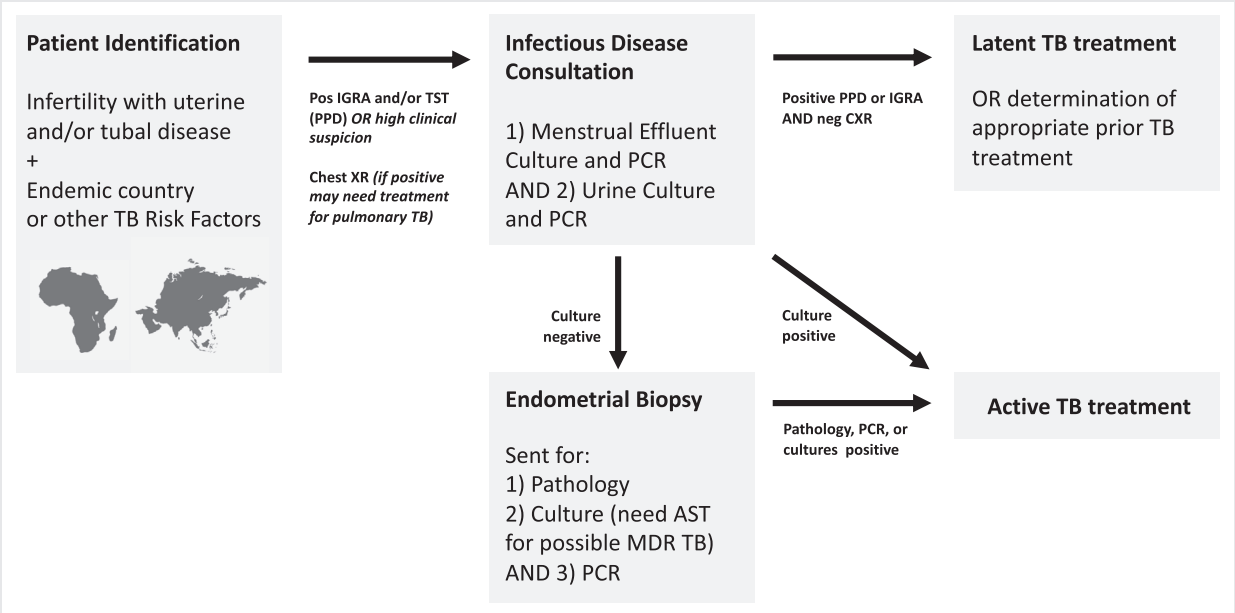
India, Pakistan, Nigeria, South Africa, Ethiopia, Kenya, Philippines, Thailand, and Brazil (16).

The diagnosis of UG TB is challenging for several reasons: low awareness of providers in low-burden settings such as the United States, the complexity of the diagnosis, lack of sensitive, definitive diagnostics, and the absence of a consensus on the diagnostic protocol. We advise further investigation despite a patient's self-report of negative TB exposure or history. Additionally, an evaluation for UG TB should take place irrespective of BCG vaccine status. Many patients from TB-endemic countries have been vaccinated for TB with the BCG vaccine; however, this should not preclude further workup or treatment for latent TB after a positive IGRA.

In a recent study, Tal et al. (8) recommends obtaining blood for an IGRA on any presenting patient who was born or had spent significant time in a TB-endemic country or who otherwise had risk factors that would qualify them for latent TB screening, such as immigration from a TB-endemic country, work in a high-risk setting (i.e., with incarcerated persons), or known TB exposure. The two licensed IGRAs in the United States are QuantiFERON-TB Gold Plus (QIAGEN) and T-Spot (Oxford). The IGRA tests are not typically conducted for active TB screening because of the possibility of false negative results (see Table 1). However, the QuantiFERON is an easy and relatively cheap blood test, which gives clinicians information about a patient's remote TB exposure by measuring the immune response to TB.

It should be noted that a negative QuantiFERON would not be sufficient to rule out active disease in a patient whose pretest probability of UG TB is high. In the event of a negative IGRA in a patient with high pretest probability, we would recommend placing a TST as well to increase sensitivity (17). If TST or IGRA is positive, or if suspicion of UG TB is high (despite a negative TST and a negative IGRA), patients should be referred for ID consultation. If the patient's history, exam, and imaging are particularly compelling, patients

FIGURE 4



Screening and referral algorithm for patients with TB-risk factors. AST = Antimicrobial susceptibility test, CXR = chest radiographs; IGRA = interferon-gamma release assay; MDR = multidrug-resistant tuberculosis; PCR = polymerase chain reaction; PPD = purified protein derivative; TB = tuberculosis; TST = tuberculin skin test

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should undergo further testing (such as biopsy for AFB stain, culture, and pathology) even if tests for TB exposure (i.e., IGRA, TST) are negative. If possible, we suggest noninvasive testing, such as urine AFB PCR (18) and culture, be sent before surgical biopsy (Figure 4). Of note, testing the urine is helpful if positive, but it is possible to have isolated genital TB with no urinary involvement.

A positive TB culture will help to confirm the diagnosis and identify or rule out drug-resistant TB and guide antimicrobial therapy. Empiric treatment of unrecognized drug-resistant TB with an inadequate regimen can lead to treatment failure and acquisition of further resistance. Therefore, it is ideal for maximizing efforts to obtain specimens that can yield an isolate for antimicrobial drug susceptibility testing whenever possible. Given the pauci-bacillary nature of UG TB and subsequent relatively poor sensitivity of AFB culture from urine, menstrual blood, and tissue biopsy, AFB cultures will often be negative despite the best efforts to make a microbiologic diagnosis by culture. As such, these patients will often be treated presumptively with a standard 6-month course of RIPE therapy. *Mycobacterium tuberculosis* PCR sensitivity can depend on sampling techniques and preparation, and as such, it is likely some patients with a positive IGRA or TST and compatible clinical syndrome (and/or consistent pathology on endometrial biopsy) will warrant TB treatment despite the lack of microbiologic (culture) or molecular (PCR) diagnosis confirmation. In some cases, ID consultants may advise empiric treatment despite a mostly negative work-up.

The prognosis of UG TB is unclear and depends on the extent and location of the disease burden before antimicrobial therapy and the timely initiation of effective treatment. Future pregnancy commonly requires IVF, given the significant and irreversible nature of tubal scarring accompanying most cases (3, 10). The clinical management of uterine scarring, which can be severe, provides additional challenges even with the use of IVF. Successful IVF pregnancies have been documented after treatment with varying rates of success (19–21). Endometrial damage from TB can be potentially further confounded through uterine procedures performed in the clinical management of pregnancy loss. There is data that preexisting chronic endometritis may further increase the risk for the development of intrauterine adhesions (22). In case 1, it is likely that the patient's dilatation and curettage procedure for the management of retained placenta after her second-trimester loss contributed to the thinning of her uterine lining and subsequent development of hypomenorrhea. Over time, remote from the procedure, the patient experienced further deterioration of her endometrial cavity, likely directly as a result of mycobacterial infection, with the endometrium ultimately unable to develop adequate thickness for embryo transfer.

Diagnosis and treatment of latent TB should also be pursued in women with positive IGRA or TST, ideally, before performing infertility treatments to prevent progression to urogenital or pulmonary TB that could be transmitted to the fetus prenatally intrapartum or in the case of pulmonary involvement to the infant postpartum. Congenital TB, such as was seen in case 2, is rare but can happen when bacilli spread through the blood from the placenta to the umbilical vein or by fetal aspiration and/or ingestion of amniotic fluid containing AFB (12). Intrauterine infection usually leads to fetal demise before delivery, such as was assumed in Patient One's second-trimester loss, which is why congenitally infected live births are rare. The decision to delay infertility treatments for latent TB therapy should be conferred on a case-by-case basis with patients with multidisciplinary discussion across infectious disease and infertility specialists involved in care.

CONCLUSION

Patients who are at risk for UG TB should be identified, screened, and treated in advance of infertility treatments to reduce the risk of adverse pregnancy outcomes.

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