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Trichomonas vaginalis Vaginitis in Obstetrics and Gynecology Practice: New Concepts and Controversies

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Abstract

Trichomonas vaginalis (TV) is the most common curable sexually transmitted infection worldwide. Annually, 7.4 million new infections are estimated in the United States, which is greater than combined new cases of *Chlamydia*, gonorrhea, and syphilis. Serious adverse reproductive health outcomes including pregnancy complications, pelvic inflammatory disease, and an increased risk of HIV acquisition have been linked to TV infection. There are several sensitive and specific diagnostic tests available, including a newly approved nucleic acid amplification test (NAAT) that utilizes the same instrumentation platform and clinical sample as *Chlamydia* and gonorrhea tests. In this article, we review TV pathogenicity, adverse reproductive health outcomes, detection, and treatment followed by clinical scenarios for which TV diagnosis may prove useful in obstetrics and gynecology practice.

Target Audience—Obstetricians and gynecologists, family physicians

Learning Objectives—After completing this CME activity, physicians should be better able to incorporate TV counseling and testing into standard clinical practice, compare and contrast available TV diagnostic tests, and manage TV in pregnant and nonpregnant women.

Incident *Trichomonas vaginalis* (TV) infections in the United States are estimated at 7.4 million annual cases, which totals more than gonorrhea, *Chlamydia*, and syphilis infections combined.[1,2] It is emerging as a serious reproductive tract pathogen, mainly affecting minorities and people living in poor or disadvantaged communities. Although TV is listed as one of Centers for Disease Control and Prevention's (CDC's) top 5 neglected parasitic infections in the United States, TV continues to be excluded from public health sexually transmitted disease (STD) control programs and is not a reportable infection.[3]

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In an article presented to the Southern Surgical Association in 1941, Brady and Reid[4] stated, "The importance of these recurring exacerbations of *Trichomonas vaginalis* vaginitis cannot be overemphasized, for in women during menstrual life the *Trichomonas vaginalis* is probably the commonest cause of leucorrhea." Such early reports in the literature highlight the pervasive and recurrent nature of TV. Indirectly, they also reflect popular thought that TV is a harmless, nuisance parasite. Yet, in recent years, serious adverse health outcomes including pregnancy complications, pelvic inflammatory disease, and an increased risk of acquiring HIV have been linked to TV infection.[5–9]

BIOLOGY

Trichomonas vaginalis was first discovered in 1836 by European physician Alfred Donné.[10] It is a single, spherical, motile, flagellated parasite with a barbed tail (called an axostyle) that resides in the urogenital tract of humans Trichomonads are anaerobic, reproduce via binary fission, and require carbohydrates (ie, vaginal glycogen) as an energy source.[11] Symptoms and signs of TV infection may be attributed to TV attachment to vaginal epithelial cells through its barbed tail, expression of a highly immunogenic surface protein (P270), and secretion of cysteine proteinases and a cell-detaching factor.[12,13] These events may lead to an intense host inflammatory response, genital tract symptoms, tissue damage, and various reproductive sequelae.

The TV genome sequence was reported in 2007, and a 2-type population structure has since emerged in a global sample of women.[14] In a study by Conrad et al,[15] participants diagnosed with TV were infected with either type 1 or type 2 in near-equal frequencies, whereas 10% of women harbored both types. Type 1 isolates were easier to detect by wet mount and may represent symptomatic patients with high parasite loads. Furthermore, this study did not find a statistically significant difference in vaginal pH or positive "whiff" test in women infected with the different types. However, type 2 isolates demonstrated a significantly higher minimum lethal concentration of metronidazole necessary to kill isolates compared with type 1, which may be responsible for metronidazole resistance.[15] Last, a double-stranded RNA virus, referred to as TV virus, was detected in 73% of type 1 isolates and 2.5% of type 2 isolates. *Trichomonas vaginalis* viruses have been shown to alter the surface expression of P270 and cysteine proteinases, which conceivably can modulate TV pathogenicity.[12,16]

REPRODUCTIVE HEALTH CONSEQUENCES

Perinatal Morbidity

Trichomonas vaginalis infection or the host inflammatory response to infection may reduce chorioamnionic membrane strength and predispose infected women to premature rupture of membranes and preterm birth (PTB).[17,18] In vitro, TV significantly impaired the biomechanical strength of human fetal membranes by reducing bursting tension, work to rupture, and elasticity in an inoculum-dependent manner.[19] Both viable trichomonads and soluble factors present in parasite-free culture media damaged membranes. Although TV's direct and indirect factors are likely involved in the pathogenesis of premature rupture of membranes, the precise mechanism remains unknown.[20]

The National Institutes of Health funded a multicenter longitudinal study in the early 1980s, which included more than 13,000 racially and ethnically diverse pregnant women, to explore the association between TV and adverse pregnancy outcomes.[21] Culture-proven TV prevalence was 12.6% overall, and 22.8% in blacks, 6.6% in Hispanics, and 6.1% in whites. After adjusting for confounders, TV was independently associated with a 30% increase in low-birth-weight (LBW) infants and a 30% increase in PTB. Furthermore, the authors attributed 3.6% of all LBW infants to maternal TV infection; in blacks, the attributable risk

was 11%; in Hispanics, 1.6%; and in whites, 1.5%.[5] Collectively, the medical community began to consider TV as more than a harmless inhabitant of the human vagina.

Subsequently, a large multicenter randomized placebo-controlled trial was conducted in the late 1990s to determine if treatment of asymptomatic TV reduced the incidence of PTB (<37 0/7 weeks) and LBW infants (<2500 g).[22] *Trichomonas vaginalis* was diagnosed by culture, and asymptomatic women were randomized to metronidazole therapy or placebo between 16 0/7 and 23 6/7 weeks of gestation. The risk of PTB was greatest among the asymptomatic women who were treated with metronidazole compared with women in the placebo group (risk ratio [RR], 1.8; 95% confidence interval [CI], 1.2–2.7). There was no difference between groups in the risk of delivering an LBW infant (RR, 1.4; 95% CI, 0.9–2.1) or delivering less than 35 weeks (RR, 1.3; 95% CI, 0.7–2.3).[22] The authors concluded that use of metronidazole to treat asymptomatic TV during pregnancy not only does not prevent preterm delivery, but also might actually increase its risk. However, the trial had several limitations, some of which the authors acknowledged. It is unlikely metronidazole triggered PTB because it was last administered before 30 weeks, whereas the greatest increase in PTB was at 35 to 36 weeks. The authors were unable to provide a plausible, evidence-based explanation for this delay. Furthermore, the dosing regimen used in this study is not used clinically to treat TV today. The standard is 2 g as a single dose, but this study used 2 g followed at 48 hours by another 2 g between 8 and 22 6/7 weeks, plus a second identical course at 24 to 29 6/7 weeks. To reach the total of 8 g used in this study, a patient would need to be treated 4 times. Although the researchers did a tremendous effort in conducting the multicenter trial, definitive conclusions regarding causation or association between metronidazole treatment of asymptomatic TV and PTB cannot be generated. Further research is required to confirm or refute the association and to prove causality.

Neonatal TV

Few data suggest that newborns may become infected with TV during birth. Trussell et al[23–25] reported the first case of newborn TV infection in 1942. Since then, there have been an additional half-dozen reports in the literature.[23–25] Transmission is proposed to occur through direct vulvovaginal contamination during birth or through ingestion of maternal secretions. If ingested, the parasite may travel through the gastrointestinal tract, deposit in stool, and subsequently contaminate the vagina. Symptoms and signs of newborn TV infection range from irritability, cloudy-white vaginal discharge, fever, urinary tract infection, and respiratory distress. The prevalence of newborn infection, however, is unknown, and hence the burden of morbidity cannot be determined accurately.

Acquisition of HIV

Trichomonas vaginalis has emerged as a cofactor for HIV transmission. Potential mechanisms for increased susceptibility include (1) recruitment of HIV target cells (ie, $CD4^+$ T cells) to the genital tract as a result of the host immune response to TV, (2) degradation of HIV-protective factors such as secretory leukocyte protease inhibitor, and (3) direct and indirect cytotoxic effects of the parasite itself.[13,26,27] *Trichomonas vaginalis* secretes a cell-detaching factor that releases epithelial cells from tissue, thereby weakening the structural integrity and defense barrier against HIV invasion.[28] *Trichomonas vaginalis* also elicits punctuate microhemorrhages in mucosal genital tract tissue, which may serve as a portal for HIV entry.

Investigators report an increased risk of HIV acquisition among female sex workers diagnosed with TV in Zaire (RR, 1.7; 95% CI, 1.1–2.8) and Kenya (RR, 1.5; 95% CI, 1.04–2.24).[8,29] In a lower-risk general African population, the odds of acquiring HIV were 2-fold higher in women who tested positive for TV by polymerase chain reaction (PCR) compared

with women who tested negative for infection (adjusted odds ratio, 2.74; 95% CI, 1.25–6.00).[9] Furthermore, among HIV serodiscordant couples, women with TV at baseline were at greater risk for HIV acquisition (RR, 2.57; 95% CI, 1.42–4.65).[6] Taken together, these data suggest that TV infection may increase susceptibility to HIV acquisition among women, especially in the black population who are at highest risk for both TV and HIV.

Upper Genital Tract Infection

Last, TV has been associated with up to 30% of acute salpingitis cases and 16% of postpartum endometritis cases.[30,31] Trichomonads have been cultured from the fallopian tubes, peritoneal fluid, and pouch of Douglas during laparoscopy. Recently, Reighard et al[32] demonstrated an increase in endometrial leukocyte subpopulations in women with culture-proven TV. *Trichomonas vaginalis* phagocytoses bacteria, yeast, vaginal epithelial cells, mycoplasmas, and herpesviruses in vitro.[33–35] These experiments have led some investigators to speculate that motile trichomonads may be capable of carrying other infectious microorganisms from the lower genital tract to the upper genital tract.[7] Although there is evidence linking TV infection to upper genital tract infection, no conclusive evidence of causality exists.[36]

CLINICAL PRESENTATION

Trichomonas vaginalis is transmitted through sexual contact (heterosexual or same-sex partners) or vertically through vaginal delivery.[37,38] The incubation period is between 4 and 28 days.[39] Men may present with symptoms of nongonococcal urethritis (ie, urethral discharge, irritation, or dysuria), whereas the most common symptom in women is a malodorous vaginal discharge. Women may also report dyspareunia, dysuria, lower abdominal pain, or vulvovaginal irritation.[40,41] However, more than 50% of women and more than 75% of men infected with TV are asymptomatic.[1,37]

Trichomonas vaginalis has been isolated from the vagina, cervix, urethra, periurethral glands, Bartholin glands, bladder, fallopian tubes, pouch of Douglas, prostate, and kidney.[1,42] Common signs in women include vulvovaginal erythema, edema, frothy yellow-gray or green vaginal discharge, elevated pH (>6), and rarely a “strawberry” cervix.

Diagnostic Tests

Trichomonas vaginalis does not survive long in acidic environments. In vitro, TV rapidly dies and lyses at pH less than 5.0.[19] Vaginal secretions in women infected with TV often have a pH greater than 4.5, and application of 10% potassium hydroxide solution may release amines, and a sharp fishy odor is detected (commonly called the “whiff” test).

Light Microscopy

Culture is the criterion standard for diagnosis of TV, although this method requires incubation of vaginal secretions for 3 to 5 days and daily microscopic examinations. It has not been routinely adopted into clinical settings because of time constraints, but it is often used in research. Immediate microscopic evaluation of vaginal secretions, a “wet-prep,” from symptomatic patients is simple, rapid, and inexpensive. A wet-prep may reveal oval or round, flagellated trichomonads and many polymorphonuclear cells. Because trichomonads can be similar in size and shape to white blood cells, jerky or spinning motions are necessary to make a diagnosis. Variables that can result in a false-negative test include low parasite load, time interval between specimen collection and microscopic examination (>10 minutes), and clinician skill.[43] As a result, almost half of the TV cases may be missed (Table 1). Of note, wet mount and culture perform best in symptomatic patients.[44]

Antigen Testing

There are 2 Food and Drug Administration (FDA)–approved point-of-care tests commercially available in the United States. Both have greater sensitivity compared with wet-prep in symptomatic patients. OSOM (Sekisui Diagnostics, Tokyo, Japan) TV is an inexpensive immunochromatographic dipstick test with high sensitivity and specificity. Results are available within 10 minutes. Affirm VPIII (Becton Dickinson, Franklin Lakes, NJ) is a DNA hybridization probe test, and results are available within an hour. In areas of high rates of loss to follow-up or in an emergency room setting, rapid testing may be useful.

Molecular Testing

Nucleic acid amplification tests, such as PCR or transcription-mediated amplification (TMA), are generally more sensitive than nonamplified tests. The same endocervical swab that is used for detection of gonorrhea and *Chlamydia* can be used to detect TV using a recently FDA-approved TMA assay (APTIMA, GenProbe, San Diego, CA). Schwebke et al[45] conducted a large, national multicenter FDA trial among 1025 women attending obstetrics/gynecology, family planning, or STD clinics to validate the NAAT performance characteristics in urine, endocervical and vaginal swabs, and ThinPrep samples. With an overall TV prevalence of nearly 12.7%, they reported superior performance of the TV NAAT (Table 1). This TMA assay has been compared with an earlier widely used research PCR assay and was found to be extremely sensitive and specific.[46] In addition to the stand-alone APTIMA TMA, LabCorp offers the same TMA assay (NuSwab) as part of its vaginitis test panel and Becton Dickinson recently completed a clinical trial utilizing strand displacement amplification technology (BD ProbeTec).

In men, wet-prep is not sensitive, and there are not any antigen tests available. *Trichomonas vaginalis* TMA is more sensitive than culture, and urethral swab performs better than urine or semen.[1,47]

Treatment Options

Medicated tampons, mercurochrome, powdered boric acid, and bisodol, alkaline, and permanganate douches were prescribed for symptomatic relief in women without cure before the introduction of metronidazole in 1959. Metronidazole and tinidazole, which are select agents of the 5-nitroimidazole group, can cure TV. Systemic therapy is preferred over topical applications to achieve adequate drug concentrations in nonvaginal sites such as the urethra and periurethral glands. Cure rate for single 2-g dose oral metronidazole is 90% to 95%, whereas tinidazole cure rate approaches 100%.[1] Tinidazole's greater cure is related to its longer half-life, higher tissue concentrations, and lower minimum lethal concentration.[48] Metronidazole-resistant TV is estimated to occur in 2.5% to 5% of cases but is considered relative. Increasing the dose of metronidazole or switching to tinidazole can usually overcome the resistance.[49,50] To prevent reinfection, sexual partners of infected patients should be treated. The Centers for Disease Control and Prevention recommends either regimen as first-line in male and female patients, but advises caution during pregnancy (Table 2).[1]

Historically, metronidazole therapy during pregnancy had been controversial. There was concern regarding teratogenicity because metronidazole readily crosses the placenta. Indeed, there are a few case reports of midline facial defects in infants born to mothers exposed to metronidazole during 6 to 7 weeks of pregnancy; however, most retrospective cohort studies do not find an association.[51,52] Moreover, a meta-analysis that evaluated 32 studies, 7 of which included first-trimester exposure, did not find metro-nidazole to be teratogenic.[53] In summary, the body of evidence suggests that metronidazole therapy during pregnancy, including the first trimester, does not lead to congenital malformations.

To reduce neonatal exposure, breast-feeding may be interrupted during metronidazole treatment and for 12 to 24 hours after the last dose. In mothers using tinidazole, it is recommended to interrupt breast-feeding for 3 days after the last dose.[1]

Overall, there remain several gaps in the literature regarding TV prevention, infection, and pathogenicity. Presumably, prevention efforts are lacking because there are insufficient data regarding reproductive harm or cost-effectiveness of screening and treatment of TV. In time, recent advancements in TV diagnostics will allow further progress of the field. However, until National STD guidelines advocate for TV screening, we present a few clinical scenarios pertinent to obstetric and gynecologic practice in which the diagnosis of TV may prove useful.

PRACTICAL APPLICATIONS OF TV NUCLEIC ACID AMPLIFICATION TESTING

Gynecologic Patients

(1) Screen and educate all women who request comprehensive sexually transmitted infection (STI) testing, regardless of age or symptoms. The sensitivity of wet mount and the rapid antigen test is slightly decreased in asymptomatic women but remains high with a NAAT.[44]

(2) *Screen and educate* "*at risk*" female patients who present for their routine scheduled preventive visit, including older (*ie*, ≥*40 years of age*) *women*. At-risk women include those with a history of an STI, new or multiple sexual partners, injection drug use, or exchange of sex for payment.[1,54] Furthermore, several investigators have demonstrated the prevalence of TV increases with age, which is unlike the epidemiology of gonorrhea and *Chlamydia*. Women in the age group 40 years or older had the highest prevalence of TV at 11% compared with 8.5% in the 18- to 19-year age category in a recent study of US women.[55]

(3) Confirmatory testing for TV diagnosed by liquid-based cytology Papanicolaou (Pap) smear in an asymptomatic nonpregnant patient. Providers may find it difficult to explain to a low-risk (ie, married, monogamous) woman that she may have an STI. Because TV can persist for years, it is usually not possible to pinpoint the time of acquisition. In addition, there is the real concern of a false-positive test result in a low-prevalence population. Options for providers include (*a*) informing the patient of the test results and positive predictive value (which depends on the local prevalence of infection) and offering the option to treat based on the Pap result alone; (*b*) performing a wet-mount examination, and if negative, then performing a TV NAAT; or (*c*) ordering a TV NAAT, which can be performed on a self-collected or provider-collected vaginal swab as a confirmatory test.

(4) Negative TV diagnosis by wet-mount in a symptomatic at-risk patient or recurrent vaginitis. Providers with access to a light microscope may wish to perform a wet mount first. This stepwise approach allows clinicians to diagnose other common causes of vaginal discharge such as yeast or bacterial vaginosis that are readily treated. However, if trichomonads are not found on wet mount, either with or without a diagnosis of bacterial vaginosis, TV NAAT may prove extremely valuable.

Obstetric Patients

(1) Screen and educate all at-risk pregnant women during the late third trimester of pregnancy. The American College of Obstetricians and Gynecologists recommends rescreening at-risk populations for *Chlamydia* during the late third trimester of pregnancy.[56] Many providers at prenatal clinics rescreen for STIs during the collection of group B streptococcus (GBS) culture at the 35th to 37th week of gestation. Testing for TV could be performed on the same vaginal or endocervical swab used for gonorrhea and *Chlamydia* NAATs. Screening at this point in gestation, as opposed to the first trimester, would serve to (*a*) decrease the overall community burden of TV, (*b*) decrease the risk of further spread of infection to new sexual partners, (*c*) decrease the patient's risk of acquiring HIV, (*d*) reduce neonatal exposure to the parasite, and (*e*) possibly decrease the risk of postpartum endometritis. Although there are no data, the 35th- to 37th-week time point was chosen to avoid any potential adverse sequelae of metro-nidazole treatment. Until a well-designed randomized controlled trial demonstrates that treatment of asymptomatic TV reduces perinatal morbidity, that is, PTB, screening for TV infection in the first trimester is not supported.

(2) Confirm resolution of TV after treatment during pregnancy. Reinfection rates during pregnancy are unknown. However, in a general female population, almost 17% of participants were reinfected within 3 months of treatment.[54] *Trichomonas vaginalis* infection remains associated with perinatal morbidity such as PTB and LBW infants. The American College of Obstetricians and Gynecologists and CDC advise test of cures for gonorrhea and *Chlamydia*; therefore, it would now seem appropriate to include TV given the availability of NAAT. The time interval between testing has yet to be determined; however, testing at least 3 weeks after treatment, as is recommended for gonorrhea and *Chlamydia*, seems reasonable.

(3) Confirmatory testing for TV diagnosed by routine Pap smear in an asymptomatic pregnant patient. The management of TV found on Pap results is the same as in nonpregnant women with a couple of additional counseling points. Patient education and counseling should include detailed information regarding test characteristics, including the false-positive rate, possible risks/benefits of treatment on the fetus and mother, and possible risks/benefits of delayed therapy on the fetus and mother. Risks/benefits should address potential concerns of late preterm delivery, HIV acquisition, newborn infection, or postpartum infectious morbidity. Treatment options during pregnancy include treating the patient and her sexual partner(s) with metronidazole, regardless of trimester or confirmatory testing, or deferring treatment until the fetus completes 37 weeks.

CONCLUSIONS

In summary, TV has emerged as a serious reproductive tract pathogen, mainly affecting minorities and people living in poor or disadvantaged communities. Incident cases in the United States are estimated to total more than gonorrhea, *Chlamydia*, and syphilis cases combined.[1,2] A recent prevalence study reported TV infection in 20.2% of black women with and without symptoms.[55] Despite these staggering statistics, trichomoniasis is not a reportable infection, nor is it a component of STI surveillance and control programs.

Trichomonas vaginalis is one of CDC's neglected parasitic infections, which are a group of 5 parasitic diseases that have been targeted as priorities for public health action. With the introduction of newer diagnostic testing, more attention can be devoted to surveillance,

prevention, and/or treatment. Because of the increasing burden of TV in certain obstetric populations, the question of whether TV screening and treatment during pregnancy improve perinatal outcomes should be readdressed. In addition, the association with pelvic inflammatory disease and HIV acquisition is troubling. No longer can we afford to continue to disregard this destructive parasite by not screening at-risk patients.

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TABLE 1

Sensitivity and Specificity of Diagnostic Tests for TV in Women

Test	Sensitivity	Specificity
Wet mount	56.0 (42.8–69.1)	100
Culture	83.0 (72.9–93.2)	100
Rapid antigen		
OSOM	90.3 (82.1–98.4)	100
Affirm VPIII	63.4 (55–65.4)	99.9 (99.4–100)
APTIMA		
ThinPrep	100 (96–100)	99.6 (98.8–99.9)
Urine	95.2 (88.4–98.1)	98.9 (97.8–99.5)
Vaginal	100 (96.7–100)	99.0 (97.9–99.5)

Data are presented as percentage (95% Cl).

Values in the table are from data reported in 3 distinct publications.[44,45,57]

TABLE 2

Treatment of TV in Pregnant and Nonpregnant Women

	Medication	Dose	Route	Frequency	Duration	Cure Rate, %
Pregnant women						
Asymptomatic or symptomatic	Metronidazole	2 g	Orally	Once		90–95 *
Treatment failure (reinfection has been excluded)	Metronidazole	500 mg	Orally	Twice daily	×7 d	
Immediate-type sensitivity (ie, urticaria, shortness of breath, wheezing)	Seek consultation with expert for desensitization					
Nonpregnant women						
Asymptomatic or symptomatic	Metronidazole	2 g	Orally	Once		90–95
Treatment failure	Tinidazole †					86–100
1st option	Exclude reinfection					
2nd option	Metronidazole	500 mg	Orally	Twice daily	×7 d	
3rd option	Metronidazole or tinidazole †	2 g	Orally	Once daily	×5 d	
Last resort	Evaluate for drug resistance; obtain susceptibility testing					
Immediate-type sensitivity (ie, urticaria, shortness of breath, wheezing)	Seek consultation with expert for desensitization					

Adapted from 2010 CDC STD Treatment Guidelines.[1]

* Higher cure rates are noted if the partner is treated.

† Safety in pregnancy has not been established.