

Trichomoniasis

Abstract

The common vaginal infection caused by **Trichomonas vaginalis** seems to play a significant role in infertility. Infection of the cervical canal prevents sperm transport by the toxic metabolic products of this organism and intrauterine infection results in scanty, sub-optimal development of the endometrium, which can repeatedly frustrate ART procedures. Pitfalls in diagnosing Trichomonal vaginal infection frequently leave the condition untreated. During an infertility workup, a concerted effort should be made to exclude the presence of this parasite. Unfortunately, in our clinical experience, over one-third of the diagnosed infections failed to respond to Flagyl therapy, which leaves behind great uncertainties about optimal therapy and management for this group.

Biology and Life Cycle

Trichomonas vaginalis is a flagellated protozoan and was first described as a vaginal pathogen during the early years of the 20th century. The organism was later documented as the cause of common infections in the lower genital canal in both males and females. There is a 50 percent chance that sexual partners will eventually exchange the parasite, a strictly anaerobic organism that survives in a wide pH range, from markedly acidic 3.5 to alkaline 8.0. The parasite is sensitive to drying effect and to atmospheric oxygen. Therefore, once having left the body, it will not survive beyond a few hours. It is believed that sexual intercourse is the most common source of transmission for this infection. Vertical transmission is also known to occur. Non-sexual transmission is theoretically possible, owing to the organism's survival in moist secretions, however, this is likely to be an exceptional means of acquisition. The infection may lie dormant for months or years.

Epidemiology

Trichomonas vaginalis has a worldwide distribution. The prevalence ranges from 5 percent to more than 50 percent in different populations. The factors associated with high prevalence are the same as for sexually transmitted diseases; poor personal hygiene, multiple sexual partners, and low socio/economic status.

Clinical Features

Over 50 percent of women with *Trichomonas vaginalis* are asymptomatic. Very few will exhibit the typical greenish, "frothy" vaginal discharge with the bright or angry red edematous appearance of the cervix. Some refer to this type of cervix as "strawberry cervix" due to its punctate appearance with multiple minute hemorrhages. When symptoms are reported, most characteristically a foul-smelling, muco-purulent vaginal discharge is present, with accompanying symptoms of dysuria and vulvar tenderness. Patchy hemorrhages can be

present on the vaginal wall and on the endocervix. Painful intercourse is not an uncommon symptom. On occasion, pelvic pain is also reported. A few patients may exhibit cervical tenderness. The severity of the symptoms correlates well with the number of polymorphonuclear leukocytes observed in the vaginal secretion. Physical examination reveals vaginal discharge. The vulva is usually red, edematous and, on occasion, excoriated.

Most of the infected males are asymptomatic. Some may exhibit a mild form of dysuria or scant urethral discharge. Still, *Trichomonas vaginalis* is believed to be an infrequent cause of the so-called non-specific urethritis and documenting it in the urethral smear does not prove that this organism is the causative agent. It is unusual to see complicated cases involving the epididymis and the prostate.

Diagnosis

The easiest way of documenting the presence of Trichomonads is using hanging-drop; that is, taking fresh endocervical samples and suspending them in normal saline solution to directly observe it under light microscopy. A typical granular appearance of the secretion with a copious number of white blood cells is a typical feature under the microscope.

The uni-cellular organism shows up with rhythmic beating of the flagella measuring 10 to 30 micro-millimeters in diameter. From symptomatic women, the organism can be recovered in as many as 85 percent of the cases. In asymptomatic women, the only reliable time to take samples for hanging-drop is at the time of ovulation, where a seemingly copious cervical mucous washes out the Trichomonads from the depths of the cervical glands. The same women often exhibit Trichomonads in the endometrial biopsy specimens. Care should be taken, however not to diagnose Trichomonads in a high endometrial biopsy specimen where the rhythmic beating of cilia of the cornual epithelial cells can be misleading.

Relation to Infertility

There is a dire paucity of literature relating Trichomonads to infertility. Since the organism is present in approximately 20 percent of the infertile population, it is important to mention several key issues that bear relevance on the reproductive process. A poor postcoital test will turn favorable following Flagyl therapy. By virtue of their mobility, Trichomonads not only infect the cervical canal, but simultaneous endometrial infection is commonly present. An endometrial infection with Trichomonads will adversely affect the development of the uterine lining. When and if a luteal phase endometrium measured on sonography is less than 10 mm in diameter and shows poor structural development, a search for bacterial and Trichomonal infections is mandatory.

Treatment options

Flagyl (Metronidazole) orally, 500mg twice daily for seven days is the standard treatment of choice. As alternate, a one-time dose of 2000 mg is often prescribed. The most important side

effects are gastrointestinal, bad taste, indigestion and when taken with alcohol, severe systemic toxicity is known to develop. Unfortunately, there is an emergence of Metronidazole resistant strains of Trichomonads. A variety of treatment regimens are offered for these patients, none with convincingly high success rates. The published results are often not reproducible. Grossman, in 1990, described a successful combination of oral and topically applied Metronidazole. In his series, the curative therapy regimen consisted of a week-long oral Metronidazole therapy, 500 mg, TID x 7 days, combined with 1 gm Metronidazole inserts for the same period of time, three times daily. In addition, he suggested rinsing the vagina with 3 percent acetic acid solution to lower the pH, assuming that the Trichomonads won't survive in a pH environment lower than 5.

It has been also suggested that increasing the dose of Metronidazole, thus increasing the plasma concentration, may produce a cure in an otherwise refractory infection. Several different dose regimens have been proposed to eradicate the Metronidazole-resistant Trichomonads. Some reports claim success with as long as a month-long therapy regimen. Most of the patients receiving these high doses of oral therapy were also treated simultaneously with 500-mg oral tablets inserted vaginally daily. Unfortunately, the literature concerning combined vaginal and orally administered Metronidazole is mostly anecdotal.¹

Livengood in 1991 reported a case of resistant vaginal Trichomoniasis that resolved following intravaginal application of nonoxynol-9. The patient involved had failed to respond to therapy with high doses of oral and vaginal Metronidazole. The author suggests that the potential usefulness of topical, nonoxynol in the treatment of vaginal Trichomoniasis warrants further study.²

Nyirjesy published a case report of a woman with a fourteen-year history of Trichomoniasis who remained uncured after many courses of Metronidazole and Clindamycin cream. Her infection eventually cleared, using Paromomycin formulated in a hydrophilic cream base, 250 mg per day for two weeks.³

A recent paper by Houang reported four cases of chronic Trichomoniasis. Favorable response was achieved with a combination of Metronidazole, 1.6 to 2.2 gm daily, combined with 1 percent Zinc sulfate douche and a 5 mg Metronidazole vaginal suppository, 1 daily for ten days. All four cases remained asymptomatic following treatment. The douches and suppositories were used prophylactically for some months, post-treatment. Unfortunately, the treatment periods are not exactly stated.⁴

Our experience with refractory Trichomonal infections is rather disappointing.

Experimentation with a 5 percent intra-vaginally intra-cervical, inter-uterine administered Metronidazole preparation, custom-compounded by our local pharmacist, has failed.

In our series we have two failures to report using Flagyl and Paromomycin combination therapy.

A number of recently encountered Flagyl-resistant Trichomonal infections allow me to estimate that approximately one-third of all the diagnosed Trichomonal infections in our clinic will resist Flagyl therapy. Several trial regimens failed in these patients; including increasing the oral dose of Flagyl to 500 mg QID for two weeks, giving the Flagyl in similar doses

intravenously for ten days or combining the oral or intravenous therapy with locally applied Metronidazole.

As far as **pregnancies** go, our clinic experience is dismal. Anecdotally, I do not recall any of my patients with resistant Trichomonas infection achieving a successful pregnancy. **As per protocol, this office routinely includes testing for Trichomonads in all of our infertility patients. Special attention is paid to patients whose ART cycles have failed in other centers as well as to patients whose suboptimal post coital tests or improperly responding endometrial linings were documented during the luteal phase.**

Case Reports

Case 1

During a lengthy infertility treatment, Trichomonas cervical infection was diagnosed. Successful treatment with Flagyl was promptly followed by a pregnancy.

Mrs. JM is a thirty-seven year old white female, who was evaluated by this office for a three and a half year history of infertility of unknown etiology. A hysterosalpingogram, performed a year before her first visit with us, showed normal findings. A semen analysis was reported to be normal. A postcoital test was reported as poor.

Prior to seeing us, Mrs. JM underwent several intrauterine inseminations with or without Clomiphene therapy.

As per routine, our office performed culture studies on the seminal fluid and on the vaginal, cervical and endometrial biopsy specimens. The seminal fluid cultures were negative for all tested organisms, including Mycoplasma, Chlamydia trachomatis, yeast, and aerobic and anaerobic bacteria. Mrs. JM's culture studies revealed a heavy growth of Mycoplasma, a heavy growth of Gardnerella vaginalis, a moderate growth of Enterococcus faecalis and the endometrial biopsy was positive for Gemella morbillorum, Peptostreptococcus asaccharolyticus and Lactobacillus acidophilus.

An immunological evaluation of Mrs. JM's serum from the first visit showed markedly elevated IgM-type antisperm antibodies against the tail section of the spermatozoa.

It was assumed that the couple's infertility was primarily due to a Mycoplasma/aerobic/anaerobic bacterial infection of the genital canal. In October 1998, both Mr. and Mrs. M. underwent a ten-day intravenous Clindamycin therapy course, which was followed up in March 1999 with a postcoital test. Fifteen hours following intercourse, the copious cervical mucous revealed only a few, sluggish spermatozoa present and the mucous was loaded with Trichomonads. Due to the presence of endometrial polyps, a D&C was performed and followed up with Flagyl therapy for two-weeks, 500 mg, three times daily for both husband and wife. A postcoital test, performed in April 1999, was judged to be passable.

In May 1999, another postcoital test, twelve hours following intercourse, showed only non-motile spermatozoa present in a copious cervical mucous. Trichomonads could not be visualized, however. At this point, Pergonal stimulation with intrauterine inseminations were planned to bypass a hostile mucous, the cause of which was unexplained. Several cycles failed and early in 2000, preparations were made for an IVF cycle.

In February 2000, a mucous test around the time of ovulation again revealed a copious number of Trichomonads. Therefore, the IVF cycle in March was combined with ten days of Flagyl therapy, starting on Day-1 of the cycle. Mrs. JM was given two ampoules of Follistim daily for eight days together with 0.1 ml Lupron daily.

On Day-11 of her cycle only 2 follicles were documented with a proper serum Estradiol level and adequate development of the uterine lining. A cervical mucous check failed to reveal Trichomonads and the sperm mucous penetration test was positive. Mrs. JM was given 10,000 units of HCG intramuscularly and was instructed to have intercourse 24 hours and 48 hours afterwards.

On April 17th, 2000, sonography confirmed an intrauterine gestation. At the time of writing this report, the pregnancy proceeds uneventfully. A recently performed amniocentesis showed a normal, female infant.

Mrs. JM's case presents a chronic Trichomonas infection, which was intermittently missed by prior examinations and was the only documented cause of the poor post coital tests and the repeatedly failed intrauterine inseminations. By combining Follistim and Flagyl therapy, suppression/elimination of the parasite allowed a spontaneous pregnancy to take place. **The case is also instructive. In situations where there is no obvious cause behind a poor cervical mucous, prior to undertaking a series of artificial intrauterine inseminations, all effort should be made to rule out an infectious cause, including the presence of Trichomonads.**

Case 2

A lengthy infertility history, with persistent chronic Trichomonas infection of both the cervix and the endometrial cavity is described, where all treatments and procedures, including artificial inseminations and IVF have failed

Mrs. ES's is a thirty-five year old who first presented to my office with a three-year history of infertility. Her medical history includes right ovarian torsion, which necessitated emergency surgery at age 17. This effectively left her with a small, rudimentary fragment of her right ovary, void of follicles.

She married in 1996 and in 1997, the couple, apparently without difficulty, achieved a pregnancy, which ended in a spontaneous abortion around nine weeks. Following the

miscarriage, Mrs. ES suffered secondary infertility and Clomid therapy was initiated in March 1998. This was followed up with artificial inseminations and HCG injections.

A semen analysis was reported to be repeatedly poor and a varicocele was corrected in July 1998.

Prior to seeing us, Mrs. ES underwent a Pergonal-stimulated cycle in December 1998, which yielded four follicles from the left ovary. This was judged to be a suboptimal response.

The endometrial biopsy cultures revealed a heavy growth of *Lactobacillus acidophilus*, *Actinomyces israelii*. Antibiotic therapy was prescribed to both husband and wife, Ampicillin, 500 mg TID for three weeks.

A postcoital test in November 1999 revealed scanty cervical mucous and a vaginal sonogram showed a poorly developed uterine lining. Ten hours following intercourse, only a few sluggish spermatozoa were present. The mucous was loaded with Trichomonads and an endometrial biopsy performed at the same time documented numerous Trichomonads within the endometrium. Flagyl therapy was initiated and in April 1999, a much-improved postcoital test was obtained. The mucous was, however still obvious for Trichomonads.

Mrs. ES then underwent a ten-day intravenous antibiotic therapy course comprised of Flagyl, 500 mg, four times daily, using an ambulatory pump system.

On May 21, 1999, following the intravenous Flagyl therapy, an endometrial biopsy and a cervical mucous test were both negative for Trichomonads. The patient was instructed to continue using vaginal Metrogel cream.

A month later, the mucous again revealed a high number of Trichomonads. At this point, a 5 percent Metrogel cream was compounded by our local pharmacist and was applied intrauterine, intracervically and vaginally twice weekly for six weeks.

For the next three cycles, the cervical mucous was tested and the endometrial lining was measured using serial sonograms. On July 21, 1999, during the time of ovulation, the cervical mucous was again heavily positive for Trichomonads and the uterine lining was 8 mm.

In August 1999, Mrs. ES underwent a ten-day Paromomycin therapy course combined with vaginal Metrogel cream. Paromomycin was given orally 250 mg, three times daily. Following the therapy, with her very next ovulation in September 1999, the cervical mucous was again evaluated and found to be heavily contaminated with Trichomonads. The uterine lining was scanty, measuring 6 mm and the biopsy showed Trichomonads within the endometrium.

At this point, I advised Mrs. Sheridan to stop pursuing fertility treatments or procedures until after I carry out a literature search for alternate drugs for Flagyl-resistant Trichomonads. The

significant findings of my literature search are listed in the reference section of this article. Unfortunately, none of the reviewed articles provided convincing enough data for me to initiate a new therapy course for Mrs. ES.

In March 2000, she was offered an IVF cycle at another center. She was advised that the Trichomonads would not interfere with her chances to achieve a pregnancy. The cycle yielded nine very good embryos; three of them were of excellent quality. These embryos were transferred, but a pregnancy failed to occur. Mrs. ES was reassured that the Trichomonads are not the cause of her implantation failures and that she should consider a second IVF cycle.

It frustrates me that I have been unable to find an effective drug therapy against Mrs. ES's Metronidazole-resistant Trichomonads. Also, the fact that she is being pushed through IVF cycles disturbs me. In my opinion, these cycles have absolutely no chance to succeed. I wish others could share my visual observations of Mrs. ES's endometrial biopsy. A lining that is half of its expected functional thickness and loaded with Trichomonads, an organism that so readily kills spermatozoa at the cervical level would also readily destroy transferred embryos of the highest quality within the endometrium.

References:

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