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Review Article

The negative influence of *Trichomonas vaginalis* on pregnancy and treatment strategies

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Abstract

Trichomonas vaginalis (TV) is a parasite that invades the urogenital tract, causing numerous pathologies. Two main genotypes can be distinguished, which differ in their response to treatment. Trichomoniasis is the second most prevalent curable sexually transmitted infection worldwide, with an estimated annual incidence ranging from 170 to 256 million cases, including approximately 25 million cases among pregnant women. This patient group is highly susceptible due to hormonal changes occurring during pregnancy. A rise in estrogen concentration causes a change in the pH of vaginal secretions, and increased epithelial exfoliation favors parasite colonization. In addition to causing pelvic inflammatory disease (PID), infertility, and cervical cancer, TV infection may also contribute to low birth weight, preterm rupture of membranes (PROM), and preterm birth (PTB). Moreover, TV is a risk factor for HIV infection. The treatment of trichomoniasis in pregnant women remains a subject of debate. Although the WHO recommends metronidazole, its use is often substituted due to concerns regarding its transplacental transport and the potential for TV resistance. This paper aims to analyze the available literature concerning the diagnosis, symptoms, complications, and treatment of *Trichomonas vaginalis* invasion during pregnancy.

Keywords: Metronidazole, *Trichomonas vaginalis*, pregnancy.

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INTRODUCTION

Trichomonas vaginalis (TV) is a cosmopolitan flagellate occurring in either trophozoite form or pseudocyst (1). Adhesion to epithelial surfaces is attributed to various adhesin proteins (2). This induces a shift to an amoeboid form with increased adhesive properties (2). TV is an extracellular parasite invading the nonkeratinizing squamous epithelium of the genital tract (1,3). It reproduces by binary fission and is glycogen-dependent (4). The protozoan can survive in pool water for three hours; therefore, pregnant women should avoid public swimming pools, lakes, and other places where the risk of infection is high. During the invasion, TV phagocytizes human cells, erythrocytes, bacteria, and fungi (1,2). The annual incidence ranges from 170 to 190 million worldwide, with 25 million cases attributed to pregnant women (5). The prevalence among women with miscarriages or ectopic pregnancies was 2,3% (6). The WHO Global Sector Strategies on HIV, Viral Hepatitis, and sexually transmitted infections (STIs) 2022-2030 aims to reduce new cases of trichomoniasis by 50% by 2030 (7). TV is primarily transmitted through horizontal transmission via coitus (approximately 70%) or perinatally. The incubation period typically ranges from 4 to 28 days. (4,8). Thanks to its surface molecules, TV induces the secretion of interleukin-1β (IL-1β), interleukin-6 (IL-6), CC chemokine ligand (CCL2), and interleukin-8 (IL-8), through the activation of reactive oxygen species (ROS), extracellular signal-regulated kinases (ERK), nuclear factor - kappa (NF-κβ) signaling pathways, and protease secretion. Proteases degrade immunoglobulins and immunogenic cytokines, triggering a specific immune response that facilitates TV survival. The primary immune cells involved in combating TV are neutrophils and macrophages, while key cytokines in this response include interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (9,10). Trichomoniasis can affect both genders; however, it is more prevalent in females (11). Risk factors include female gender, pregnancy, dark skin color, older age, candidiasis, HBV infection, genital warts, diabetes mellitus, unemployment, low socioeconomic status, substance abuse, or having two or more sexual partners within the last year, in which case the probability is nine times higher. Risk of trichomoniasis is 20 times higher in people who have early sexual contact. Personal hygiene (especially genital powdering), the phase of the menstrual cycle, and the use of hormonal contraception postpartum also play a role (4, 8, 12-20). TV is also prevalent in women with cervical intraepithelial neoplasia (21). Research on a population of Finnish, Dutch, Belgian, and Chinese women showed an increased risk of cervical cancer in women with TV and vice versa (3). Another susceptible group is teenagers due to behavioral factors, underdevelopment of the uterus, or poor eating habits (12). Trichomoniasis symptoms rarely occur premenarche or postmenopause (22). Abbail et al. discovered that women with a previously diagnosed STI have a significantly higher risk of future TV infection (21, 23). Compared with other high-income countries like Great Britain, the occurrence of TV is higher in the USA (19). Other high-prevalence countries include South Africa, Madagascar, Zambia, Mozambique, Malawi, and Zimbabwe (24). The highest infection rate in the USA is among non-Hispanic black women – 13.3%, which is up to ten times the number of Mexican-American (1.8%) or non-Hispanic white women (1.3%) (11). The lowest rates are observed in Asia, where TV is the most common sexually transmitted parasite (13.6%) (24). This may be due to differences in access to medical care or cultural and economic factors. Early detection of TV is crucial in managing pregnancy because it can help alleviate the risk of preterm birth (PTB) (25). The basic diagnostic method is wet mount examination under a light microscope using Gram or Giemsa staining. Trophozoites are identified based on their size (10-20 μm), oval or pear-like . A positive result indicates the presence of motile TV (22). However, this method has lower sensitivity compared to TV culture, which, while more accurate, is also more time-consuming and financially burdensome (26,27). The first Nucleic Acid Amplification Test (NAAT) for diagnosing vaginal trichomoniasis was approved by the United States Food and Drug Administration (FDA) in 2011. NAAT is characterized by high sensitivity and specificity and can be used to examine vaginal secretions and urine samples (11). In most cases, the symptoms of trichomoniasis are benign and nonspecific and include itching, irritation, and reddening of the genital area, dysuria, dyspareunia, and a foamy vaginal discharge of yellow to grey-green color with pH> 4.5 (4,28). The mucus contains a higher concentration of immunoglobulin A (IgA) and C-reactive protein (CRP) (9,29). Trichomoniasis is usually asymptomatic and, if left untreated, may contribute to fallopian tube pathologies, pelvic inflammatory disease (PID), and infertility (30). Hence, patients should

be periodically examined. TV is often associated with the co-occurrence of pathogenic organisms such as *Mycoplasma hominis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Human Papillomavirus* (HPV), and *Human Immunodeficiency Virus* (HIV), all of which pose individual threats to pregnancy (7,31). Infection of the mother can lead to complications at every stage of pregnancy (32). Treatment methods for trichomoniasis are widely debated. The WHO emphasizes the importance of metronidazole as the first line of treatment (33). It is effective during pregnancy but also increases the chances of PTB and low birth weight, so administration should be withheld until the end of the first trimester (34). Another drug considered for treating the disease is clindamycin; however, it also affects the genital microflora (35). A combination of nifuratel and nystatin is gaining increasing interest. When used locally, these agents do not cross the blood-brain barrier and lack systemic effects. Additionally, they exhibit efficacy against fungal infections caused by Candida albicans and Candida glabrata (36,37). However, despite successful eradication, reinfection remains a concern if the sexual partner has not undergone treatment (38). Although the overall occurrence of STIs is decreasing, trichomoniasis remains common (13). Many patients are asymptomatic, and the infection may persist for 3-12 months or longer in cases of misdiagnosis, mistreatment, or lack of treatment (11,13). It is important to remember that with reinfection, symptoms may appear weeks, months, or years post-primary invasion (11). Asymptomatic women are the main reservoir (39). TV primarily exists in two main genotypes; however, in the Democratic Republic of Congo, eight distinct genotypes (A–H) have been identified through Restriction Fragment Length Polymorphism (RFLP) analysis of the actin-coding gene. This method involves enzymatic digestion using Hind II, Mse I, and Rsa I restriction enzymes (40). According to WHO, TV infection is a sensitive marker of high-risk sexual behavior (13). There are few documented cases of TV infection outside the urogenital tract because the parasite seems specific to this site (1,40).

Predisposing factors in pregnancy

Rising levels of progesterone act as suppressants on the local cellular immune mechanisms by immunomodulating T lymphocytes (41). Inflammation caused by TV induces an immunologic response characterized by the release of inflammatory cytokines, elastases, and matrix metalloproteinases (MMPs) (25). MMPs degrade collagen and weaken the fetal membrane. Alongside inflammatory cytokines and prostaglandins (PGs), they may contribute to cervical shortening, uterine contractions, preterm rupture of membranes (PROM), and PTB (25,28). Progesterone inhibits the NF-κB pathway, which is connected to apoptosis, cell proliferation, inflammation, and the control of innate and adaptive immune responses at the start of labor. NF-κB partially induces uterine contractions and labor; and its early activation can lead to complications such as miscarriage or preterm birth (PTB). It plays a key role in regulating the levels of cytokines in the amniotic fluid, fetal membranes, placenta, uterine muscles, and cervix, with these cytokine concentrations being notably higher during both preterm and full-term labor. IL-1β synthesis leads to the activation of the apoptotic pathway in host cells, and preterm labor due to this factor often occurs around 18–22 weeks of gestation (WG) (9) . Interleukin-10 (IL-10) helps regulate NF-κB by lowering TNF-α, IL-6, and PG levels in fetal membranes. A lack of this cytokine results in increased lipopolysaccharide (LPS)-induced synthesis of IL-6 and TNF-α, which has been associated with PTB. Increased activity of NF-κB during pregnancy may lead to fetal development disturbances, such as slow growth rate, miscarriage, or PTB. NF-κB levels are negatively regulated during pregnancy in the T lymphocytes present in the peripheral blood of the mother. NF-κB is thus a key molecule in regulating cytokine, growth factor, hormone, and infection factor-mediated PTB, as in the case of TV (42). Other changes during pregnancy include increased levels of estrogen, fetoprotein, and placental growth factor, which lower the host's defensive capabilities, enabling embryo implantation and maintenance of pregnancy (27). Fetoprotein secreted by the fetal liver into the amniotic fluid may impede T lymphocyte proliferation (43). Bagga et al. showed that pregnant women have a diminished population of lactic acid bacteria in the genital tract, leaving them prone to infection (28). Brotman et al. concluded that 90% of women with trichomoniasis have a vaginal pH> 4.5, consistent with bacterial and TV infection

and their combination (13,44). In patients with a significant genital microflora imbalance, the risk of PROM increases five-fold (45). Furthermore, fluid retention in the mother's body and compression of lymphatic vessels during pregnancy exacerbate vaginal exudate, making it more difficult to differentiate between STIs and physiological increases in vaginal discharge during pregnancy. Additionally, genetic differences between the mother and fetus require the suppression of certain maternal immune functions to maintain pregnancy. This immune suppression helps prevent maternal rejection of the fetus but also increases the mother's susceptibility to infections. Interestingly, this suppression reduces the likelihood of autoimmune diseases, as the maternal immune system is less likely to attack its own tissues during pregnancy (43).

Symptoms

Women usually present with mild symptoms such as dysuria, dyspareunia, vaginitis, vulvitis, a "strawberry" cervix, and postoperative complications (2,4). The dominant symptom is lower abdominal pain; however, half of the patients (50%) do not experience any symptoms. In addition to elevated pH, the vaginal discharge may be yellowish to grey-green in color and of foamy consistency, sometimes resembling pus (4,22). When mixing the discharge with 10% potassium hydroxide, putrescine is released along with a fishy smell, a method referred to as the whiff test (4,46). This symptom is often accompanied by intense vulvitis, urethritis, and inflammation of Skene's glands. In some cases, the ectocervix may be hyperemic with red dots. Schiller's test may be used to examine tissue aggression, revealing an irregularly stained cervix with a tiger stripe pattern during speculum examination (43). PTB and low birth weight rates in an infected woman are % higher than in a healthy woman, attributed to the weakening of the chorionic membrane and an accelerated rate of cervical shortening (4,43,47). Invasion may lead to cervical erosions and infertility, cervical cancer (1.9 times higher risk), and PID (1-4). TV infection accounts for 30% of acute salpingitis and 16% of postpartum endometritis (4). Notably, 72% of women suffering from trichomoniasis belong to the community state type IV (CST-IV) group Brotman et al. characterized by a low number of protective *Lactobacillus spp*. and an increased number of anaerobic bacteria (46,48). The protozoan exerts its cytopathic effect by releasing proteins responsible for creating membrane pores with pH-dependent activity, optimal at 5.8 pH (46,49). ATP, a product of cell death, increases the concentration of inflammatory cytokines and stimulates the chemotaxis of neutrophils and mast cells (9). TV employs the binding of LPS to galectins 1 and 3 as a mechanism to regulate host immunity. The concentration of galectin-3 in umbilical cord blood shows a positive correlation with the incidence of preterm birth (PTB) and low birth weight (50). Surface receptors are thought to be the main virulence factor allowing adhesion to host cells (51). Diagnosis should not be based solely on clinical symptoms due to their nonspecificity. Increased CRP levels may increase the risk of postpartum depression (9,52). Recovering from trichomoniasis does not grant lasting immunity (50). Recurrent infections are frequent and occur in 5–37% of cases, and a microflora imbalance is a predictive factor in miscarriage and PTB risk even if it has recovered (3,35,51). The degree of risk associated with pregnancy is negatively correlated with the week of gestation in which a flora imbalance was discovered (25). A positive screening test result for microflora imbalances between 26 and 32 weeks of gestation is associated with a statistically significant increase in the risk of preterm birth (PTB) (35). Additionally, a positive test result during the second trimester correlates with a 2.0 to 6.9-fold increased risk of pregnancy complications (35,45). There has been no correlation between TV infection and chorioamnionitis in the third trimester (12). When an infection contributes to a miscarriage, IL-1 is the first to be involved. Upregulating the synthesis of cyclooxygenase-2 (COX-2) by monocytes and macrophages stimulates uterine contractions (25). Elevated concentrations of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) are responsible for the abundance of these immune cells, together with granulocytes and dendritic cells. Long-lasting TV invasion during pregnancy may lead to neutrophil migration and an increase in TV lipoglycan (anti-TvLG) IgG immunoglobulins in vaginal secretions of patients without an adverse outcome pathway (AOP) (9). Martin et al. suggested that TV infection is positively correlated with *M.*

hominis and *Ca. M. girerdii*, mostly in TV-positive women (53,54). Coinfection with *Ca. M. girerdii* more frequently presents with intense itching compared to a sole TV invasion (55). *M. hominis* was isolated from amniotic fluid and fetal membranes of women after PROM, suggesting that the microorganism is responsible for initiating PG synthesis at the start of PTB. TV acts as a Trojan horse for this species of bacteria. Coinfection significantly hinders nitric oxide (NO) synthesis by macrophages, disabling the host defense (1). *M. hominis* also enhances TV's adhesive properties. Fifty-eight percent of *M. hominis* isolated from TV carries the goiC gene, considered a bacterial virulence factor connected to amnionitis and PTB. The TV growth rate is increased when coupled with *M. hominis*. Recent studies have shown that women with bacterial vaginosis (BV) caused by *M. hominis* have an increased concentration of amines and short-chain fatty acids (SCFA). SCFAs, including acetic acid, butyric acid, and propionic acid, play a significant role in various immune responses by inhibiting the synthesis of inflammatory cytokines, modulating the migration and phagocytic activity of immune cells, and inducing apoptosis in cells such as neutrophils (9,46).

Treatment

Designing treatment strategies for pregnant women infected with TV is challenging and constantly evolving. The previous approach included a single dose of 2 g metronidazole orally (19). The 2015 WHO Recommendations presented a modified approach with a seven-day regimen of 500 mg metronidazole taken orally twice daily, which helps to reduce the risk of adverse effects (3,43). Although tinidazole is stronger than metronidazole, it is not available in generic form and in some cases, is not reimbursed in the USA (31). For pregnant women, metronidazole is preferred orally, though it can also be used as a vaginal suppository (35,43). Attempts to utilize metronidazole cream topically were unsatisfactory (21). The advantage of metronidazole is its protective effect on the endangered lactic acid bacteria population in the genital region (35). It permeates the cell membrane of a trophozoite by simple diffusion and undergoes anaerobic reduction in the hydrogen some of TV by an enzyme, pyruvate-ferredoxin dehydrogenase. Free nitrate radicals bind with DNA, causing strand breaks and cell death. However, decreased activity of flavin reductase has been reported in metronidazole-resistant TV (21). Current treatment relies almost solely on 5-nitroimidazole derivatives, raising concerns about arising resistance. The added of dithiocarbamates with metronidazole has demonstrated a 3- to 10-fold increase in response to metronidazole-sensitive TV and a 10- to 20-fold increase in response to metronidazole-insensitive TV. Metronidazole-chalcone conjugates showed a fourfold increase in efficacy against resistant strains compared to metronidazole alone. Albendazole and coenzyme B12 have shown the best efficacy when combined with metronidazole or tinidazole in treating resistant TV strains (31). Trichomonas in the TV1 genotype are more sensitive to metronidazole and are frequently infected with viruses from the Totiviridae family, which increases pathogenicity (1). Some studies showed increased metronidazole resistance in TV when co-infected with *M. hominis*. While metronidazole is effective, it also carries the risk of PTB and low birth weight (34). Common adverse reactions include headaches, dizziness, diarrhea, disulfiram reaction, and metallic taste. Vomiting after administration has also been reported, in which case the dose is repeated two days later. Metronidazole allergy is rare and manifests as hives, rash, itching, bronchospasm, and fever (31,35). Some case reports suggest a potential association between metronidazole and the development of median line malformations during the first 6-7 weeks of pregnancy, though the evidence is insufficient. Although 5-nitroimidazoles are attributed to carcinogenic, mutagenic, and teratogenic properties, satisfying evidence is lacking (4,31). Metronidazole has contributed to PTB in high-risk groups during the second trimester (10,34). A randomized controlled trial in Uganda on 4000 patients reported a 17% decrease in PTB and a 47% reduction in birth weight deficiencies after administering a single 2 g dose of metronidazole orally (38). Metronidazole resistance in HIV-negative women ranges from 2.2-13% but can usually be overcome by re-treatment with a higher dose or the same dose (3,21,39,56). Clinical metronidazole resistance is defined as the absence of cure after two cycles of treatment. Resistance patterns have been reported in women from South

Africa (20). Often, an improvement is observed, followed by relapse within three weeks, suggesting that 5-nitroimidazole resistance is relative rather than absolute (31). A more recent drug administered orally is secnidazole, a new generation 5-nitroimidazole with a longer half-life (17 hours) than metronidazole (7-8 hours) or tinidazole (12-13 hours) (3). However, it is not safe for use in pregnancy (3). Clindamycin has anti-inflammatory properties and a broader spectrum compared to metronidazole, being effective against microorganisms associated with bacterial vaginosis (BV) such as *Mobiluncus spp*. and *Mycoplasma spp*. Clindamycin has a similar treatment success rate to metronidazole but also kills lactic acid bacteria, impeding treatment. Clindamycin is more effective in topical form. BV is associated with subclinical endometritis, so if the pathogen crosses the blood barrier, topical treatment may no longer be viable. Late topical administration up to 32 weeks gestation is accompanied by a higher chance of PTB and neonatal infections. Topical treatment should be applied in the first half of pregnancy (35). Nifuratel belongs to the nitrofuran class and is used for various urogenital infections (36). Its antiprotozoal activity and effectiveness against Gram-positive and Gram-negative bacteria, as well as fungi, make nifuratel a useful tool in a gynecologist's practice (56). It exhibits a bacteriostatic effect and a bactericidal effect in high doses. It is readily absorbed in the gut and partially metabolized in the liver. It lacks activity against systemic bacterial infections and does not affect bacteria in the blood or tissues outside the urogenital tract (36). Nystatin is an organic antibiotic synthesized by *Streptomyces noursei,* active against *Candida spp*. (albicans and non-albicans). Its bioavailability when administered orally is low, and it is excreted almost entirely unchanged in the feces. The nifuratel-nystatin combination is gaining popularity due to its synergistic effect. In the treatment of vaginitis, it promotes a restorative effect on the microflora and helps prevent reinfection. Unlike clindamycin, this combination spares lactic acid bacteria. When used locally, the drug combination does not cross the blood-brain barrier and does not result in significant systemic effects. A linear dose-effect relationship is observed. The lowest effective dose is 250 mg nifuratel and 100,000 I.U. nystatin, while the most effective dose is 500 mg nifuratel and 200,000 I.U. nystatin once per day for five days (36). A seven-day regimen yielded a 93.15% cure rate according to Amsel's criteria - used for diagnosis of bacterial vaginosis - and after thirty days, the rate was 87.67% (57). No teratogenic adverse effects were observed, so the combination might be safe for use in pregnancy (36,56). The exact mechanism of action of the nifuratel-nystatin combination remains unclear, but nifuratel acts via coenzyme-A and inhibits glucose metabolism. Its effectiveness is comparable to that of 5-nitroimidazoles. Sexual abstinence should be maintained during treatment. Adverse effects are generally mild and self-limiting, including hives, itching, and contact dermatitis (36,56). In a sheep model, a single dose of cytokine suppressive anti-inflammatory drugs (CSAID) silenced the LPS-induced immunity response, mediated by NF-κB and p38 mitogen-activated protein kinase (MAPK), responsible for PTB. In other animal model studies, the combination of ampicillin-dexamethasone-indomethacin (AMP/DEX/INDO) suppressed IL-1β, TNF-α, prostaglandin E2 (PGE2), and prostaglandin F2 (PGF2α) but did not affect chorioamnionitis or MMP expression. The AMP/DEX/INDO combination suppresses the inflammatory state and prolongs pregnancy (35). Miltefosine and nitazoxanide show activity against TV in vitro. Miltefosine is effective against metronidazole-sensitive and insensitive TV isolates (20). It acts as an antiproliferative agent and induces ultrastructural changes leading to apoptosis (31). Miltefosine's safety in pregnancy has not been established, and nitazoxanide is appropriate for local use only due to low bioavailability when administered orally (21). Pentamycin, synthesized by *Streptomyces penticus*, is a polyene-macrolide antibiotic. It is effective in treating trichomoniasis independent of metronidazole sensitivity. A 22 µM concentration can eliminate 100% of parasites after one hour of treatment. It was approved for intravaginal use and is an alternative to metronidazole (31). If antibiotic treatment is withheld until late pregnancy, changes in the cervix, myometrium, decidua, placenta, and extraplacental membranes make it unlikely that antibiotics will be helpful (35). Overuse of antibiotics contributes to microflora imbalances and microorganism resistance, which is of dire consequence. A positive diagnostic test for TV persisting for a long time may be due to reinfection, mistreatment (such as drug resistance), or impeded TV nucleic acid elimination (36,38). Pregnant women are more sensitive to medication, so adverse effects should always be considered. Probiotic supplementation is

recommended to protect the vaginal microbiome (27). Antibiotic use in pregnancy is associated with gut flora imbalances in neonates, which may be the basis for autoimmune diseases such as asthma and atopic dermatitis (35). Despite trials conducted in the 20th century, there is currently no vaccine available against Trichomonas vaginalis (TV). The use of mechanical contraception has been shown to reduce infection rates among women. A study involving Kenyan teenagers demonstrated that unprotected coitus is correlated with an increased transmission of TV (21). Due to frequent recurrence, screenings should be conducted once every three months from the start of treatment. A 2015 study concluded that the NAAT examination should be conducted once every three weeks after the end of treatment (3).

Conclusion

Considering all the presented evidence, it is clear that the issue of TV infection during pregnancy should not be underestimated. Owing to the fact that its presence is often asymptomatic, it is crucial to examine patients regularly. Both therapy and diagnosis are constantly evolving, and special care should be given to the risk groups. Despite its adverse effects, the use of metronidazole as a golden standard for many infectious ailments has led to the development of resistance and the need for an alternative. Many options are available; however, for pregnant women, the best choice, based on additional benefits, seems to fall on the combination of nifuratel and nystatin. It is important to note that this combination needs to be used carefully to avoid the development of resistance.

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