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# Isolation of *Trichomonas vaginalis* and Investigation of Metronidazole Susceptibility in Patients with Vaginal Discharge

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## Abstract

*Trichomonas vaginalis* is one of the most important vaginitis agent in the world. Metronidazole is the most frequently chosen antimicrobial agent for trichomoniasis treatment. The aim of this study to investigate the in vitro metronidazole susceptibility of *T. vaginalis* strains isolated from clinical samples.

This study was performed with 130 female patients with vaginal discharge. Informed consent was obtained from each patient included in the study. Samples were taken from the posterior fornix of the cervix with a sterile cotton swab, were placed in trypticase-yeast extract-maltose (TYM) medium and transported to the microbiology laboratory. Firstly, the presence of trophozoites in the sample was determined with direct microscopic investigation between glass slides. If T. *vaginalis* trophozoites were detected, they were passaged to a new medium and pure *T. vaginalis* trophozoites were isolated. The metronidazole susceptibility of isolates was investigated with the microdilution method. Isolates with minimum lethal concentration (MLC) above 50 µg/mL were accepted as resistant.

In one of all samples *T. vaginalis* was detected by direct microscopic investigation. From samples in TYM cultures, three T. *vaginalis* isolates were identified. For two of the isolated *T. vaginalis* strains, the MLC value was 1.56 µg/ml, while the other had an MLC value of 3.12 µg/ml. In light of these data, all the three *T. vaginalis* isolates were identified to be metronidazole susceptible.

It should not be forgotten that *T. vaginalis* is an important causative agent of vaginitis.

**Keywords:** *Trichomonas vaginalis*, metronidazole, microdilution.



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## 1. Introduction

*T. vaginalis* is a flagellated protozoan with an undulating membrane that moves by rotation around itself and causes trichomoniasis in human. It emplaces in the vagina in women and in the urethra in men. Trichomoniasis is generally transmitted from human to human by sexual contact. For this reason, the incidence of the disease is higher in sexually active women (Saygı G, 2009).

In the whole world, it is the most commonly observed parasite species among sexually-transmitted infections. The parasite does not have a cystic form, and disease occurs via the trophozoites. Apart from sexual relations, transmission may occur from flush toilets, pools that are not maintained and are attended by many people, non-sterile gynecological examination tools, shared bathing suits and toilet paper. Infected mothers may infect the infant during vaginal birth (Unat EK at al., 1995).

*T. vaginalis* infection progresses as a foamy, yellow-green color, watery mucous, creamy texture and malodorous discharge in women. Speculum examination observes painful, red, hemorrhagic and edematous vaginal mucosa. Trichomoniasis may appear as a simple infection, but if not treated it may cause early rupture of membranes, pelvic inflammatory disease, tubal infertility risk in women and low birth weight of neonates (Petrin D at al., 1998). The incidence of the infection varies according to the lifestyle of the society and sociocultural structure (Altıntaş K., 2002).

Laboratory diagnosis of infection may use samples taken with a sterile swab from the posterior fornix or urethral discharge in women, while urine samples or prostate fluid may be used in men. In addition to direct microscopy and stained preparate investigation commonly used in many laboratories, centers with adequate diagnostic capacity may use culture methods (Sönmez C. at al., 2018). In cases that are asymptomatic or in situations where the parasite is not observed in vaginal discharge or in epidemiological studies, serologic diagnostic methods may be used (Saygı G, 2009). Diagnosis may also benefit from molecular methods (Ertabaklar H. at al., 2011). Due to ease of application and low cost, direct microscopy is frequently used for investigation (Ertabaklar H. at al., 2009). This method is undoubtedly the cheapest, easiest to apply and most rapid method; however, it does not have optimal reliability due to its low sensitivity (Özcel MA, 1997).



Detection of *T. vaginalis* generally does not require smear preparates (Korkmaz M. at al., 2011). Culture methods take time and have high cost, while attempts have been made to increase sensitivity with staining methods using Giemsa, acridine orange, May-Grunwald, aceto-orcein, hematoxylin-eosin and Papanicolaou due to the low sensitivity of direct microscopy (Özcel MA. at al., 2007).

For diagnosis of *T. vaginalis*, culture methods are accepted as the gold standard Sorvillo F, at al., 2001). To be able to identify the parasite with culture methods, 1-10 microorganisms in the sample appear to be adequate for detection (Wang J. 2000) The most appropriate temperature for growth is 37 °C, with parasites able to grow in 9-12 hours at the earliest. Many culture media have been defined for the *T. vaginalis* culture. The most important media include cysteine-peptone-liver-maltose (CPLM) medium, trypticase-yeast extract-maltose medium (TYM), modified Diamond (MD) medium, modified thioglycolate medium, Kupferberg medium, plastic envelope method (PEM-TV) and in pouch TV culture methods (Toker R.,1995; Daldal N. at al., 1997). Medications recommended and frequently used for trichomoniasis treatment are the 5-nitroimidazole compounds of metronidazole and tinidazole (Ertabaklar H. at al.,

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2016). Metronidazole is the most frequently chosen drug for trichomoniasis treatment, though the presence of isolates resistant to metronidazole has been reported in several countries and the need for new treatment approaches has been emphasized (Matini M. at al., 2016). Resistance of trichomoniasis to antiparasitic medications is frequently studied with the microdilution method.

The aim of this study was to investigate and isolate *T. vaginalis* from cervical swab samples taken from women attending our university hospital with vaginal discharge complaints, and to research the *in vitro* metronidazole resistance of the isolates.

## 2. Materials and methods

The study received ethics committee permission from Gaziantep University Clinical Research Ethics Committee with the date 19.06.2018 and protocol number 267. This study was performed with vaginal samples taken from 130 patients with vaginal discharge complaints our university hospital gynecology and obstetrics clinic from 1 October 2020 to 1 March 2021. All patients were in the sexually active period and no limiting factors were identified apart from vaginal discharge complaints. . Informed consent was obtained from each patient included in the study. Vaginal discharge samples were taken during gynecological examination (in the lithotomy position, with a speculum inserted) using sterile cotton swabs (Microcult, Ankara, Türkiye) on the cervix posterior fornix. Samples were placed in fluid medium within a screw-cap sterile tube (ISOLAB, Eschau, Germany) and inoculation was performed separately for each patient. As a growth medium, TYM containing 20% sterile horse serum (OXOID, Basingstoke, UK) was used. The TYM was prepared by dissolving 0.5 mg L-cysteine HCl, 0.1 g ascorbic acid, 0.4 g K2HPO4, 0.4 g KH2PO4, 10 g trypticase, 2.5 g maltose, and 10 g yeast extract in 300 mL distilled water (Daldal N. at al., 1997). Then, 0.1 ml of sterile antibiotic solution containing 10,000 unit/mL penicillin, 10 mg/mL streptomycin and 25 µg/ml amphotericin-B (SIGMA, St. Louis, USA) was added to each 2 mL medium and stored at +4 °C. The cervical swab samples were inoculated on TYM separately for each patient, transported immediately to the laboratory and rapidly investigated. Swab samples were examined with direct light microscopy between glass slides for direct examination (Figure 1, Figure 2). Samples examined with direct microscopy were then placed in an incubator at 37 °C. Then all samples were examined directly between 24-48 hours later and growth checks were made in the incubator for 10 days duration. Preparates with growth were subcultured on fresh TYM at 48-hour intervals and after at least three passages, the isolated *T. vaginalis* strains were re-studied in order to detect the presence of metronidazole resistance.



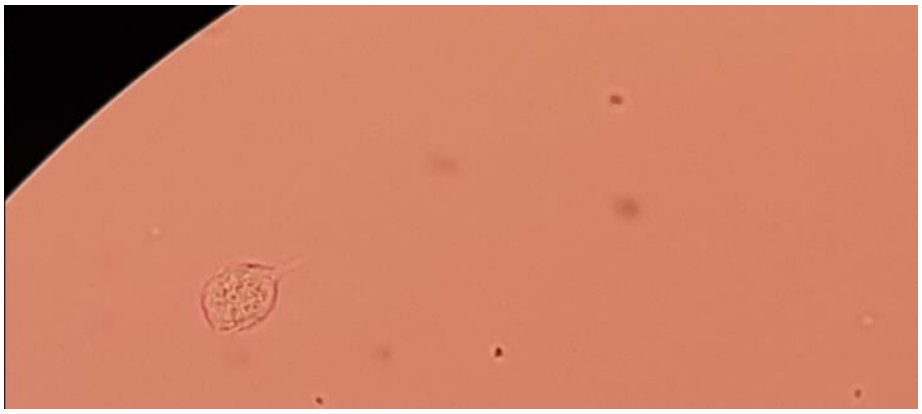

**Figure 1.** Image of motile *T. vaginalis* trophozoite in light microscope

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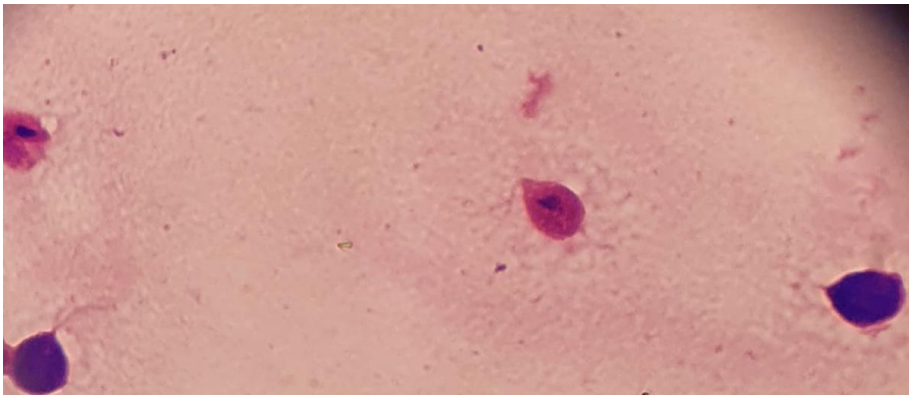

**Figure 2.** Microscopic image of *T. vaginalis* trophozoites stained with Giemsa

Antimicrobial susceptibility test of the growing isolates were performed for metronidazole using the microdilution method. Sterile metronidazole powder was used (Goldbio, St. Louis, USA) for the susceptibility test. To dissolve the powder of metronidazole, dimethyl sulfoxide (DMSO) was used as a solvent (EMPLURA, Billerica, USA). Available DMSO was sterilized by straining through 0.22 µm filter paper. With the aim of control and standardization, metronidazole-susceptible *T. vaginalis* (ATCC 30188) and metronidazole-resistant (ATCC 50143) *T. vaginalis* standard strains were used. Metronidazole resistance was investigated with the microdilution method as previously described (Ertabaklar H. at al., 2016). For dilution, TYM medium containing 20% sterile horse serum was used. Microdilution was performed in 96-well U-floored sterile cell culture plates. Metronidazole was placed in the wells with final concentrations of 200, 100, 50, 25, 12.5, 6.25, 3.12, and 1.56 µg/ml. Inoculum containing a standard density of protozoa were set to $10^4$/mL protozoa by counting on a Thoma slide (Ertabaklar H. at al., 2016). Additionally, sterile medium not containing antibiotic and trophozoites was placed in one well to check the sterility of the medium. Another well only had isolate added without antibiotics to check whether the strain maintained viability in the antibiotic-free medium. *T.vaginalis* trophozoites were incubated with different concentrations of metronidazole (200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56 µg/ml) in aerobic conditions at 37 ºC. Forty-eight hours later, a drop sample was taken from each well with a sterile Pasteur pipette and examined between a slide and coverslip for mobile trophozoites under a direct light microscope. Isolates in the first well with the highest concentration where mobility was not observed were later subcultured onto fresh TYM to check viability. After 48-hours of incubation with metronidazole concentration above 50 µg/ml, isolates containing viable trophozoites were accepted as resistant, while isolates without viability observed were accepted as susceptible (Gökmen AA at al., 2016; Schwebke JR at al., 2006; Kirkcaldy RD at al., 2012)



Statistical analysis was performed by SPSS for Windows, version 22.0 (IBM Corp. Released 2013). P value < 0.05 was considered as statistically significant.

## 3. Results

When the files of 130 patients included in the study were investigated, two of these patients were monitored for infertility (1.5%) and six were monitored for malignancy (4.6%). Additionally, one patient (0.8%) had a vaginal abscess observed during a gynecological examination, while one of the two patients monitored for infertility was identified to have a tubo-ovarian abscess. The patients included in the study were aged 20-68 years, with the mean

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age identified as 39 years (Mean±SD; 39.02 ± 10.93).

Direct microscopic examination of 130 cervical swab samples obtained from patients identified *T. vaginalis* trophozoites in one sample (0.77%), while no *T. vaginalis* trophozoites encountered in 129 samples (99.23%). Culture positivity using the TYM medium for *T. vaginalis* was identified as three out of 130 samples (2.3%), with no *T. vaginalis* growth in 127 samples (97.7%). Direct microscopic examination method detected only one (33.33%) of the three samples growing in culture. (Table 1).

**Table 1.** Comparison of direct microscopy with culture method

| | ***T. vaginalis* culture** | |
|---|---|---|
| **Direct microscopic presence of *T. vaginalis*** | **Negative** | **Positive** |
| **Negative** | 127 | 2 |
| **Positive** | 0 | 1 |
| **Total** | **127** | **3** |

All three *T. vaginalis* strains isolated from cultures were identified as being susceptible to metronidazole (MLC <50 µg/ml). Two of these three isolates had MLC values of 1.56 µg/ml, while one had an MLC value of 3.12 µg/ml (Table 2).



**Table 2.** MLC values of *T. vaginalis* isolates

| | **MLC (µg/mL) of Metronidazole** | **Resistance status** |
|---|---|---|
| **Isolate 1** | 1.56 | Susceptible |
| **Isolate 2** | 1.56 | Susceptible |
| **Isolate 3** | 3.12 | Susceptible |

## 4. Discussion

The trichomoniasis agent of *T. vaginalis* is the most frequently observed and treatable protozoan among sexually-transmitted pathogens after viral and bacterial agent in the world. Interest in *T. vaginalis* has increased as it is a commonly observed infection, and is associated with serious health problems like AIDS, cancer, etc. (Prokopi Mat al., 2011). According to the 2015 treatment guide for sexually-transmitted diseases, an average of 3.7 million people are affected by *T. vaginalis* in the USA (Workowski KA at al., 2015). Studies using direct microscopic investigation and a variety of culture methods predicted that 2-50% of the population in Africa carry the infection (Mairiga AG at al., 2011).

Studies in different regions of Turkey have reported that the infection spreads at different rates depending on the lifestyle and sociocultural structure of individuals and differences between the patient groups studied. Daldal et al. found no significant difference between diagnostic methods in a study of 33 sex workers (Daldal N at al., 2002). They reported that a total of 42.4% *T. vaginalis* positivity was identified with at least one of the methods of direct microscopy,

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culture and Giemsa staining. In a study of 220 patients attending with vaginal discharge complaints, Ertabaklar et al. researched *T. vaginalis* with direct microscopic investigation and culture (TYM) methods and identified *T. vaginalis* in 5.45% of cases with direct microscopy and 7.27% of cases with culture methods (Ertabaklar H at al., 2004). A study of married patients by Keleştemur and Kaplan identified the incidence of *T. vaginalis* was 3.8% by using any of the direct microscopy, Giemsa staining and culture methods (Keleştemur N at al., 2010). Değerli et al. reported 1.9% *T. vaginalis* rate with direct microscopic investigation and 1.5% with the culture method in their study (Degerli S at al., 2011). In İstanbul, Polat et al. investigated the presence of *T. vaginalis* in samples taken from 207 patients with suspected trichomoniasis and identified *T. vaginalis* positivity in two samples (0.97%) using at least one of the direct microscopy and culture methods (Polat E at al., 2011). Sankur and Ertabaklar assessed vaginal swab samples from 150 patients in a hospital providing tertiary health services in terms of the presence of *T. vaginalis* in their study (Sankur F at al., 2018). They identified the presence of *T. vaginalis* in two of 150 samples with direct microscopic investigation (1.3%) and in two samples with at least one of the other methods (2%). Yazısız et al. researched the presence of *T. vaginalis* in women with complaints of vaginal discharge attending a clinic in a university hospital, and reported it was present in 1.9% of patients with microscopic investigation and did not identify proliferation in culture due to technical reasons associated with *T. vaginalis* being identified with PCR (Yazısız H at al., 2020).

As can be seen, along with variations from region to region, the incidence of *T. vaginalis* displays wide variability according to differences in the study groups. Our study was not a field screening study; all 130 patients attended a gynecology clinic in a university hospital. Three of these patients had proliferation in TYM medium and the culture positivity rate was identified as 2.3%. Only one of the three positive culture samples had the parasite observed with direct microscopic investigation (0.77%). This shows that the chance of detecting the parasite with the TYM culture method is higher than when using direct microscopic examination. However, as we detected positivity in only three patients, this number was not adequate to perform a statistically significant comparison. When the rate we identified is compared with other studies in similar populations, it is similar; in fact, it appears some studies identified higher rates of positivity. Additionally, the identification of a lower rate of positivity than expected may be associated with the COVID-19 pandemic affecting the whole world. As such, this pandemic led to many mandatory restrictions in public areas. In the course of attempting to protect against the COVID-19 pandemic by abiding by personal distance rules, closure of locations in public areas like shopping centers and restaurants, public toilets, baths/hammams, and brothels with the aim of minimizing interpersonal contact, and extra care with personal hygiene and cleaning rules, in fact protection was provided against several other infectious diseases. Additionally, we did not reach the desired and targeted number of patients due to the mandatory reduction of contact in hospitals and numbers of clinics with the aim of preventing infection, and lower numbers of patients examined due to the pandemic. Unfortunately, this negatively affected our chance of detecting positivity. In spite of this, the 2.3% rate of positivity identified in the study is consistent with the rates identified in other studies performed before the pandemic.



In our study, two of the cases with *T. vaginalis* positivity identified were 28 years old and one was 31 years old. The three patients were married and had single partners. This is consistent with the 17-40 year age interval when sexual activity occurs most intensely (Degerli S at al., 2011). Different studies of *T. vaginalis* infections having different distributions in different age groups may be associated with the different socioeconomic conditions and lifestyles of the people in these case groups (Jarallah HM, 2013).

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In our study, one of the 28-year old patients with *T. vaginalis* growth was being monitored due to a tubo-ovarian abscess and information was obtained that she had received infertility treatment for nearly two years. This patient was also the only patient with trophozoites observed with direct microscopic investigation. This leads to the consideration that the probability of observing the parasite with direct microscopic investigation is increased in the presence of a dense parasitic load. Literature information indicates that the *T. vaginalis* infection increases the risk of pelvic inflammatory disease and tubal infertility (Cates W at al., 1993; Wilkinson D at al., 1999). For this reason, it was considered that the cause of this patient's infertility and tubo-ovarian abscess might be linked to *T. vaginalis*. This information was immediately shared with the clinician, and comprises data that will guide the patient's treatment.

In spite of the current use of 5-nitroimidazole derivatives for trichomoniasis treatment, *T. vaginalis* has been known to develop resistance against metronidazole for nearly 50 years (Edwards D, 1993; Poppe WAJ, 2001; Sobel JD at al., 1999). Cases resistant to metronidazole have been reported from several countries over many years (Meri T at al., 2000; Matini M at al., 2016). The results of the research appear to identify very different rates of metronidazole resistance linked to the region in which the study was performed and the chosen cases. Perez et al. reported that two out of 91 *T. vaginalis* strains (2.4%) isolated from sex workers and women attending a gynecology clinic in Spain from 1995-1999 were resistant to metronidazole (Perez S at al., 2001). These researchers accepted the resistance limit as 50 µg/ml and defined this as low-level resistance. Schmid et al. found that two out of 82 *T. vaginalis* strains (2.4%) were metronidazole-resistant (Schmid G at al., 2001).

A study by Schwebke and Barrientes defined 50-100 µg/ml MLC as low-level resistance, 200 µg/ml MLC as moderate resistance and >400 µg/ml MLC as high-level resistance under aerobic conditions (Schwebke JR at al., 2006). In this study, Schwebke and Barrientes found that the in vitro metronidazole resistance of *T. vaginalis* in the United States of America was 9.6%. Similarly, from 2009-2010, Kirkcaldy et al. (Kirkcaldy RD et al., 2012) accepted 50-100 µg/ml MLC as low-level resistance, 200 µg/ml MLC as moderate resistance and >400 µg/ml MLC as high-level resistance, similar to the study by Schwebke and Barrientes. This study in America accepted isolates with MLC above 50 µg/ml as resistant and reported that 4.3% of *T. vaginalis* strains isolated from women had low-level (50-100 µg/ml) metronidazole resistance.



In Turkey, a study by Ertabaklar et al. (Ertabaklar H at al., 2016) used MLC values of 75 µg/ml for aerobic environments and 15 µg/ml for anaerobic environments. The results of this study reported that three out of 40 *T. vaginalis* isolates (7.5%) were metronidazole-resistant. This 7.5% rate of metronidazole resistance appears to be much higher than the resistance rates reported from other countries (Ertabaklar H at al., 2016; Meri T at al., 2000). Gökmen Aksoy et al. (Gökmen AA at al., 2016) studied the drug resistance of a single clinical *T. vaginalis* strain against a variety of drugs with the microdilution method. They found that the MIC and MLC values in the 72nd hour were 50 µg/ml and 100 µg/ml for metronidazole/ornidazole; 200 µg/ml and 400 µg/ml for pantoprazole; and 400 µg/ml and 800 µg/ml for esomeprazole, respectively. According to these values, they reported that the isolate in the study was susceptible to metronidazole.

Taking previous studies by Schwebke and Barrientes (Schwebke JR. at al., 2006) Kirkcaldy et al. (Kirkcaldy D at al., 2012) and Gökmen Aksoy et al. (Gökmen AA at al., 2016) in our country as a reference, isolates with MLC higher than 50 µg/mL were accepted as resistant. In light of this data, all the three *T. vaginalis* strains we isolated were accepted as metronidazole-susceptible. When compared with other studies, our inability to find a metronidazole-resistant

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strain may be due to the patient number in our study and our inability to access adequate isolate numbers. We think studies performed with a broader scope will obtain metronidazole-resistant strains.

Our literature review indicates that our study has the feature of being the first to perform isolation and metronidazole resistance studies for *T. vaginalis* in Gaziantep province and in our region.

In conclusion, it should not be forgotten that *T. vaginalis* is an important causative agent of vaginitis. The easiest, fastest and cheapest method for diagnosis of *T. vaginalis* infection is to search for trophozoit in a fresh sample by direct microscopic examination. However, it should be kept in mind that false negative results may occur in samples containing a small number of trophozoids with this method.

In selected cases, it will be beneficial to support the microscopic diagnosis with culture method in the advanced clinical microbiology laboratories. Metronidazole resistance should be taken into account in the case of treatment failure

A limitation of our study is that we could not reach the number of patients that we had targeted due to the fact that interpersonal contact was reduced to a minimum level because of Covid-19 pandemic. We believe that, isolation of *T. vaginalis* agents by culture method and performing antibiogram can guide the treatment by reducing unnecessary use of antimicrobials.

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