SHORT REPORT

Trichomonas vaginalis, endometritis and sequelae among women with clinically suspected pelvic inflammatory disease

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ABSTRACT

Objective To ascertain the prevalence of *Trichomonas vaginalis* and investigate associations between trichomoniasis, endometritis and sequelae among women with pelvic inflammatory disease (PID).

Methods We assessed the prevalence of trichomoniasis identified via wet mount and its association with histologically confirmed endometritis, infertility and recurrent PID among 647 women in the PID Evaluation and Clinical Health (PEACH) study. Participants were treated for clinically suspected PID and followed for a mean of 84 months for incident sequelae. Analyses were adjusted for age, race, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and bacterial vaginosis. Additional adjustments were incorporated for history of infertility (models of pregnancy and infertility), history of PID (recurrent PID), and self-reported partner treatment and intercourse between baseline and 30-day follow-up (persistent endometritis).

Results *T. vaginalis* was present in the vagina of 12.8% of women. The odds of having endometritis at baseline were twice as high among women with trichomoniasis as compared with those without (adjusted OR (AOR): 1.9, 95% CI 1.0 to 3.3). Persistent endometritis was highly prevalent at 30 days (52.1%) and more common among women with baseline trichomoniasis (AOR: 2.6, 95% CI 0.7 to 10.1), although non-significantly. Infertility and recurrent PID were more common among women with trichomoniasis, while rates of pregnancy and live birth were lower.

Conclusions *T. vaginalis* was frequently isolated from the vagina of women with PID in the PEACH cohort. Wet mount microscopy for the identification of motile trichomonads was standard practice at the time of the PEACH study, but likely resulted in an underestimation of true *T. vaginalis* prevalence. Our findings of modest, although non-significant, prospective associations between trichomoniasis and sequelae are novel and underscore the need for additional investigation into whether *T. vaginalis* may play an aetiological role in adverse reproductive and gynaecological outcomes.

INTRODUCTION

Trichomonas vaginalis is an anaerobic flagellated protozoan commonly isolated from the female genital tract. Trichomoniasis is the most common curable STD globally.[1] In the USA, approximately 3.1% (95% CI 2.3% to 4.3%) of women are affected, a prevalence similar to chlamydia and greater than gonorrhoea or syphilis, with markedly higher rates among non-Hispanic blacks and postadolescent women.[2] Trichomoniasis is asymptomatic in more than 70% of affected women and has been associated with increased transmission, prolonged duration of infection, and an increased risk of myriad gynaecological and obstetric sequelae, including pelvic inflammatory disease (PID), HIV transmission and acquisition, cervical neoplasia, infertility, and adverse pregnancy outcomes such as low birth weight, premature rupture of membranes and preterm birth.[3]

PID is the infection and inflammation of upper genital tract structures caused by ascension of microbes from the lower genital tract. PID frequently leads to subsequent adverse gynaecological and reproductive sequelae, including infertility, ectopic pregnancy, recurrent PID or chronic pelvic pain in up to 45% of women. One-third to half of PID cases are attributable to gonorrhoea and chlamydia, while the remainder are of unknown aetiology. Studies of *T. vaginalis* and PID are limited and none has examined the relationship between trichomoniasis and histologically confirmed PID. Moreover, no prospective studies have investigated the association between trichomoniasis and subsequent infertility.

Our objectives were to ascertain the prevalence of *T. vaginalis* and investigate associations between trichomoniasis and short-term (persistent endometritis) and long-term (infertility, pregnancy, live birth and recurrent PID) sequelae among women with clinically suspected PID.

METHODS

Data for these secondary analyses are from the PID Evaluation and Clinical Health (PEACH) study, a multicentre, randomised clinical trial designed to compare the effectiveness of inpatient and outpatient antimicrobial therapy for prevention of adverse sequelae among 831 women with mild-to-moderate clinically suspected PID. The PEACH study methodology has been described in detail elsewhere.[4] Baseline *T. vaginalis* status was ascertained via identification of motile trichomonads on saline microscopy of lateral vaginal wall secretions. PID was histologically confirmed using previously published study criteria for endometrial samples.[5]

Logistic regressions, adjusted for age, race, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and bacterial vaginosis, were used to examine associations between *T. vaginalis* and sequelae through an average of 84 months of follow-up. The true prevalence of trichomoniasis was approximated using the Rogan-Gladen estimator. All analyses were conducted using SAS V.9.4.

RESULTS

T. vaginalis prevalence in the lower genital tract was 12.8% at baseline. It was more frequently isolated from the lower genital tract than *M. genitalium* (9.5%) and less frequently than *C. trachomatis* (21.5%) or *N. gonorrhoeae* (20.2%). Assuming that wet mount has a sensitivity of 51%–65% and specificity of 100% compared with a nucleic acid amplification test (NAAT) for the identification of *T. vaginalis* from vaginal samples,[6] we estimated the true prevalence of trichomoniasis to be 19.7%–25.1%. Assuming the same sensitivity but a slightly lower specificity of 95%, the true prevalence likely falls in the range of 13%–17%.

The prevalence of acute endometritis was 27.1% at baseline. Women with trichomoniasis were more likely to have histologically confirmed endometritis at baseline both before (OR: 2.3, 95% CI 1.5 to 3.8, p<0.01) and after adjusting for age, race, *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium* and bacterial vaginosis (adjusted OR (AOR): 1.9, 95% CI 1.0 to 3.3, p=0.04). Persistent endometritis at 30-day follow-up was observed among 52.1% of women with baseline endometritis. In models adjusted for age, race, concurrent STIs, self-reported partner treatment and intercourse between baseline and 30-day clinic visit, women testing positive for *T. vaginalis* experienced persistent endometritis more frequently (AOR: 2.6, 95% CI 0.7 to 10.1).

Sequelae were common among women in our study cohort, including endometritis at 30 days (36.5%), infertility (25.0%), recurrent PID (24.7%) and chronic pelvic pain (38.0%). Persistent endometritis, infertility and recurrent PID were more common among women with trichomoniasis, while rates of pregnancy and live birth were lower, although findings were of borderline significance or non-significant using α=0.05. These findings were consistent irrespective of upper or lower tract STI coinfection status (table 1).

DISCUSSION

T. vaginalis was frequently isolated from the lower genital tract of women with clinically suspected PID. This rate was similar to that reported in earlier studies and is substantially higher compared with women in the general population. When accounting for the inferior sensitivity of wet mount relative to newer diagnostic techniques such as NAAT, we estimate that the true prevalence of trichomoniasis may be 20%–25% among the PEACH cohort. Women testing positive for vaginal *T. vaginalis* had twice the odds of histologically confirmed endometritis at baseline compared with those without, and persistent endometritis was highly prevalent (52.1%) at 30 days. This finding, while not statistically significant, is consistent with the mounting body of cross-sectional evidence that *T. vaginalis* may play a role in the pathogenesis of PID.[3 7–9] The prevalence of endometritis was lower among women without concurrent genital tract infections in our subgroup analyses, 12.0% vs 27.1% in the complete study cohort, a finding which may indicate a synergistic role for multiple pathogens in the development of PID.

Trichomoniasis has been associated with multiple adverse obstetric and gynaecological outcomes in cross-sectional analyses, but to date no prospective studies have investigated the temporality of these relationships. Although we observed non-significant associations using α=0.05, we observed higher rates of infertility and recurrent PID and lower rates of pregnancy and live birth among *T. vaginalis*-positive women. Analyses restricted to women without concurrent STIs had lower numbers of sequelae, which may have further limited the statistical power of tests among this subgroup. Our finding is consistent with earlier

Table 1 Sequelae among women testing positive vs negative for *Trichomonas vaginalis*

Among all women (n=647)						
Outcome	***T. vaginalis* (n=83) n (%)**	**No *T. vaginalis* (n=564) n (%)**	**Crude OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Persistent endometritis at 30 days*	16/52 (30.8)	46/342 (13.5)	2.9 (1.5 to 5.6)	<0.01	2.6 (0.7 to 10.1)	0.17
Pregnancy†	40/80 (50.0)	326/556 (58.6)	0.7 (0.4 to 1.1)	0.15	0.7 (0.4 to 1.1)	0.14
Live birth	30/32 (93.8)	240/253 (94.9)	0.8 (0.2 to 3.8)	0.79	0.6 (0.1 to 3.2)	0.55
Infertility‡	20/80 (25.0)	94/556 (16.9)	1.6 (0.9 to 2.8)	0.08	1.6 (0.9 to 3.0)	0.11
Recurrent PID§	19/77 (24.7)	118/539 (21.9)	1.2 (0.7 to 2.0)	0.58	1.2 (0.7 to 2.1)	0.62
In the subgroup of women without upper or lower tract *Chlamydia trachomatis*, *Neisseria gonorrhoeae* or *Mycoplasma genitalium* (n=384)						
Outcome	***T. vaginalis* (n=42) n (%)**	**No *T. vaginalis* (n=342) n (%)**	**Crude OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Persistent endometritis at 30 days*	2/27 (7.4)	10/196 (5.1)	1.5 (0.3 to 7.2)	0.62	1.2 (0.2 to 6.3)	0.81
Pregnancy†	14/40 (35.0)	185/338 (54.7)	0.4 (0.2 to 0.9)	0.02	0.5 (0.2 to 1.0)	0.05
Live birth	10/12 (83.3)	140/149 (94.0)	0.3 (0.1 to 1.7)	0.18	0.3 (0.1 to 2.0)	0.23
Infertility‡	12/40 (30.0)	62/338 (18.3)	1.9 (0.9 to 4.0)	0.08	1.9 (0.9 to 4.1)	0.10
Recurrent PID§	11/37 (29.7)	69/326 (21.2)	1.6 (0.7 to 3.3)	0.24	1.4 (0.6 to 3.0)	0.41

All models are adjusted for age, race, *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium* and bacterial vaginosis. Pregnancy, live birth and infertility models are additionally adjusted for self-reported history of infertility at baseline, and recurrent PID models are additionally adjusted for self-reported history of PID.

*Persistent endometritis was defined as the presence of acute histological endometritis (≥5 neutrophils and ≥1 plasma cell) at both baseline and 30-day clinic visits.

†Pregnancy was defined by a physician diagnosis or positive blood or urine β-hCG test.

‡Infertility was defined as a lack of conception despite 12 or more months of unprotected intercourse or inconsistent contraceptive use.

§Recurrent PID was defined as self-report of one or more episodes of PID during follow-up and was verified by medical record review where possible.

β-hCG, human chorionic gonadotropin; PID, pelvic inflammatory disease.

case–control analyses that reported significantly increased odds of prior *T. vaginalis* infection among women with infertility and a higher prevalence of trichomoniasis among infertile women compared with controls.[10]

A limitation of this investigation is that women were enrolled based on signs and symptoms consistent with PID, so our results extend only to women with similar clinical characteristics. The analyses herein are a secondary exploration of data from the PEACH study, and consequently available data are not optimised for the study of trichomoniasis and its sequelae. Endometrial samples were not assessed for the presence of *T. vaginalis* in the PEACH study, so we are unable to report the prevalence of trichomonads in the endometrium or determine the degree of concordance between the lower and upper genital tracts. Available endometrial data are cross-sectional, so we are unable to ascertain the timing of *T. vaginalis* infection relative to that of other STDs and whether infection preceded endometritis.

Our *T. vaginalis* prevalence estimate may be low and subsequent effect estimates attenuated because of the use of wet mount microscopy for the diagnosis of trichomoniasis. Wet mount is frequently used in clinical and research settings because it is inexpensive, fast and non-labour-intensive compared with alternatives such as culture and PCR. A trade-off of this convenience is the lower sensitivity of wet mount relative to culture (51%–65%) and PCR (52%).[6] Diagnostic methodologies for the identification of trichomoniasis have improved significantly in the two decades since PEACH study enrolment began, with the development of newer techniques including immunochromatographic capillary flow enzyme immunoassay dipsticks and NAATs. These newer technologies have shown striking improvements over wet mount and culture in test sensitivity (82%–100%) while retaining very high specificity (95%–100%).[6] Nonetheless, these techniques are rarely used to guide clinical practice due to cost and treatment delays while waiting for results. Future studies requiring accurate estimates of *T. vaginalis* prevalence, treatment effectiveness and clinical impact should consider these newer diagnostic techniques because of their superior performance.

T. vaginalis infection is common among women in the general population and even more so in women with clinically suspected PID such as those in the PEACH study. The Centers for Disease Control and Prevention named trichomoniasis, the most common curable STD in the USA, as one of five neglected parasitic infections for targeted public health intervention including heightened surveillance, prevention and treatment initiatives. Trichomoniasis is readily treatable, but the high rate of asymptomatic infection contributes to the burden of disease and increases risk for the acquisition and spread of other STDs and HIV. Additional prospective studies are needed to further delineate the possible role of *T. vaginalis* in the pathogenesis of PID and its sequelae. Moreover, it is important for future studies to assess whether treatment of trichomoniasis would lessen the burden of sequelae among women with PID.

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