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Prevalence and Clinical Significance of *Mycoplasma genitalium* in Gynecologic Patients

Oluwatosin Goje[1]*, Jessian L Munoz[1], Frederick S Nolte[2] and David E Soper[3]

[1]*Obstetrics, Gynecology and Women's Health Institute, Cleveland Clinic Desk, Cleveland, USA*
[2]*Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston SC, USA*
[3]*Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston SC, USA*

Abstract

Objective: *Mycoplasma genitalium* has been recognized as a cause of male urethritis, and there is now evidence suggesting it causes cervicitis and pelvic inflammatory disease (PID) in women.

Methods: Prevalence, risk factors and co-infections with other sexually transmitted pathogens were collected in a cross-sectional study looking at 400 women at the gynecologic clinics of a university medical center in the United States. Bacterial vaginosis and trichomoniasis were diagnosed using Amsel's criteria, gram stain and trichomonas culture respectively. Cervicitis and PID were clinically diagnosed. After testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, the residual cervical swab transport medium (Gen-Probe/Hologic®) was stored at -70°C. Stored samples were later analyzed for *M. genitalium* by a research use only transcription-mediated amplification assay using procedures similar to those established for APTIMA Combo2 assay for *C. trachomatis* and *N. gonorrhoeae* (Gen-Probe/Hologic®).

Results: The overall prevalence of infection with *C. trachomatis, N. gonorrhoeae, T. vaginalis and M. genitalium* was found to be 7.8%, 1.8%, 10.43% and 8.9%, respectively. Prevalence of *M. genitalium* was comparable to that *of C. trachomatis* and greater than the prevalence of *N. gonorrhoeae*. Univariate analysis of *M. genitalium* status showed that participants with lower condom use had an increased probability of *M. genitalium* (p=0.037).

Conclusion: Prevalence of *M. genitalium* was comparable to *C. trachomatis* in our study, but more research is needed to clarify pathogenicity.

Keywords: *M. genitalium*; *C. trachomatis*; *N. gonorrhoeae*; Risk factors

Introduction

Although *Mycoplasma genitalium* is well documented as a causative pathogen in non-gonococcal, non-chlamydial urethritis in men; the manifestations of infection in women are less well described. There is now evidence suggesting it causes cervicitis and pelvic inflammatory disease (PID) in women [1]. One of the major limitations encountered in the study of *M. genitalium* is that it is fastidious and difficult to culture. Although there is no U.S food and drug administration (FDA) approved commercial detection system, the availability of molecular methods for research and commercial purposes has altered our ability to derive valid information about the pathogenicity of this bacterium. There have been more studies in recent years researching into its pathogenicity and treatment [2-6]. The most recent Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases treatment guidelines discussed it under emerging issues [1]. *M. genitalium* has been implicated in endometritis, cervicitis and pelvic Inflammatory Diseases (PID) and it may have significant effect on reproductive health and pregnancy outcomes [7,8].

Therefore, the purpose of this study was to investigate the prevalence of *M. genitalium* in women aged 18 and older attending our clinic, determine the percentage of women diagnosed with cervicitis and PID who were *M. genitalium* positive. We wanted to identify women at high risk for *M. genitalium* and examine the relationship between *M .genitalium* and other known sexually transmitted infections (STIs).

Methods

A cross-sectional study was performed following the approval of the study protocol by the Institutional Review Board (IRB) at a tertiary university medical center. Participants who presented to the Obstetrics and Gynecology clinics for care were included if they were 18 years or older and sexually active. Participants who met criteria were consented, enrolled and interviewed by the research coordinator. History, pelvic and speculum examination, cervical and vaginal samples were collected by the health care provider performing the gynecologic exam.

Saline microscopy to diagnose bacterial vaginosis (BV), candidiasis and *Trichomonas vaginalis* was performed and documented by the health care provider. Diagnosis of PID was made based on the CDC guidelines [1]. A patient was diagnosed with cervicitis if the clinician found: mucopurulent cervical discharge/mucopus and/or friable cervix that bled easily on application of a swab. The principal investigator confirmed the diagnosis of PID by reviewing the data collected by physicians. For this study, a *T. vaginalis* culture was performed using the In-Pouch® system, BV diagnosis was initially made using Amsel's criteria and confirmed with gram stain. Gonorrhea and or Chlamydia infection was diagnosed using nucleic acid amplification test (NAAT). An endocervical swab contained in the APTIMA® Unisex swab specimen Collection Kit was used to collect patient swab specimen per manufacturer's protocol and was processed for gonorrhea and chlamydia NAAT.

***Corresponding author:** Oluwatosin Goje, Obstetrics, Gynecology and Women's Health Institute, Cleveland Clinic, Desk A81, 9500 Euclid Avenue, Cleveland, OH 44195, USA; Tel: 440-315-3809; E-mail: Gojeo@ccf.org

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M. genitalium transcription-mediated amplification (TMA) assay

After testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, the residual cervical swab transport medium (Gen-Probe/Hologic®) was stored at -70°C. The specimens were analyzed for *M. genitalium* by target capture, amplification by TMA and detection by the hybridization protection assay in a manner similar to procedures established for APTIMA Combo2 assay kit protocols established for *C. trachomatis* and *N. gonorrhoeae* (Gen-Probe/Hologic®). Primers and probes and target capture oligonucleotides were designed by Gen-Probe/Hologic® to be specific for *M. genitalium* and were designed to be used with the reagents that the same formulation as APTIMA Combo2 as previously described [9,10].

The *M. genitalium* assay was performed on the Tigris system. The reagents were provided to us for research use only. The threshold for positive reactions was set at ≥ 40,000 relative light units [10]. This cutoff was validated in our laboratory with a panel of 25 positive and 25 negative specimens previously tested at the University of North Carolina at Chapel Hill with the same *M. genitalium* TMA assay. The positive and negative percent agreement between the results of the tests was 92% and 100%, respectively.

Statistical methods

The documented prevalence of *M. genitalium* in literature varies; it depends on communities and clinics where research was performed. We assumed a 20% prevalence of *M. genitalium* similar to Gaydos et al.'s Baltimore study [11]. Numerical measures was summarized by mean and standard deviation when the values are approximated by a normal distribution; otherwise summarized by median and interquartile range. Normality determined by visual inspection of histograms and normal QQ plots. Categorical values summarized by frequency and percentage. Statistical methods to each study aim are described below.

Prevalence of *M. genitalium* estimated as the proportion observed in the sample with a 95% confidence interval based on a normal approximation of the proportion. Potential risk factors for *M. genitalium* determined from univariable comparisons of potential risk factors with *M. genitalium*. Comparisons performed by t-test, Wilcoxon test, or chi-square test of association, depending on the level of measurement of the potential risk factor. Associations of morbidity (cervicitis and PID) evaluated using univariable chi-square tests of association. Associations of *M. genitalium* with gonorrhea, chlamydia, and bacterial vaginosis and trichomonas infection evaluated using univariable chi-square tests of association.

Results

A total of 400 women participated in the study with majority identifying as African American (71.8%) and unmarried (93.5%). Majority of the cohort were non-smokers (77.5%). 76.5% self-reported sexual debut by age 18 years, 93.6% had male sex partners. Majority (80.25%) of the cohort agreed that condom use during sexual intercourse prevents STI but only 19.75% consistently used condoms during sexual intercourse. In our cohort, 9% never used condoms during sexual intercourse. There was a past history of STI in our cohort, with 40.5% endorsing a past history of chlamydia, and 5.75% being HIV infected. Vaginal discharge followed by abdomino-pelvic pain were the most commonly reported symptoms (28.25% and 14.5%, respectively) and rate of cervicitis and PID were 11% and 7%, respectively.

The overall prevalence of infection with *C. trachomatis, N. gonorrhoeae*, *T. vaginalis* and *M. genitalium* was found to be 7.8%, 1.8%, 10.43% and 8.9%, respectively.

There was no difference in the median age between *M. genitalium* positive and negative participants; 25 years versus 24 years. (p=0.84). Majority of *M. genitalium* positive patients self-identified as African Americans and were unmarried (83.3% and 91.7%, respectively). There was no difference in race, marital status, educational level or tobacco history between *M. genitalium* positive women and *M. genitalium* negative women. There was no difference in sex partner preference and total lifetime partners between both groups.

Twenty four of the participants screened positive for *M. genitalium,* the percentage was 8.9% with a 95% confidence interval of (5.9%, 13.1%). Looking at the *M. genitalium* cohort, 79.2% did not smoke cigarette, 62.5% had sexual debut between 15-18 years of age and all had male sex partners. 45.8% had a previous history of chlamydia, 16.7% history of gonorrhea and 12.5% were HIV positive. Based on presenting symptoms, 20.8% complained of vaginal discharge and 20.8% pelvic or lower abdominal pain. 8.3% complained of dyspareunia, 4.2% complained of vaginal spotting/bleeding (Table 1). None of the

Symptoms	Total	N (M. gen negative)	Percent	N (M. gen positive)	Percent	P-value (f)
Vaginal Discharge	400					0.63
No	287	176	72.13	19	79.17	
Yes	113	68	27.87	5	20.83	
Burning on urination	400					>0.99
No	398	243	99.59	24	100	
Yes	2	1	0.41	0	0	
Lower abdominal/pelvic pain	400					0.35
No	342	212	86.89	19	79.17	
Yes	58	32	13.11	5	20.83	
Pain with sexual intercourse	400					>0.99
No	361	218	89.34	22	91.67	
Yes	39	26	10.66	2	8.33	
Vulvo-vaginal itching	400					>0.99
No	398	243	99.59	24	100	
Yes	2	1	0.41	0	0	
Vaginal Bleeding	400					0.70
No	367	223	91.39	23	95.83	
Yes	33	21	8.61	1	4.17	

f: Fisher's exact test for count data

Table 1: *M. genitalium* was not associated with any specific gynecologic symptoms.

Factor	Total	N (M. gen negative)	Percent	N (M. gen positive)	Percent	p-value (f)
Race	400					0.11
African American	287	161	65.98	20	83.33	
Other	113	83	34.02	4	16.67	
Use of Condoms	392					0.81
No	99	58	24.58	5	20.83	
Yes	293	178	75.42	19	79.17	
History of condom use	400					0.037
Never	35	15	6.53	5	20.83	
Sometimes	137	89	36.33	6	25	
Most of the time	149	96	39.18	6	25	
Always	79	44	17.96	7	29.17	

f: Fisher's exact test for count data

Table 2: Univariable comparisons by Mycoplasma status.

participants complained of dysuria, increased urinary frequency or vaginal itching. We also looked at the association of *M. genitalium* with other STIs diagnosed during the same gynecologic visit (co-infection), and 4.2% of *M. genitalium* patients had gonorrhea, 8.3% had chlamydia, 12.6% trichomonas and 58.3% had BV in addition to *M. genitalium*. One *M. genitalium* patient was diagnosed with PID and 4 diagnosed with cervicitis.

Only one risk factor showed a significant relationship with *M. genitalium* in a univariate comparison by mycoplasma status (Table 2). Participants with lower condom use had an increased probability of *M. genitalium* (p=0.037). There was no association between the presence of *M. genitalium* and a previous history of STIs. When we looked at the relationship of *M. genitalium* and other STIs in our study, it appears that *M. genitalium* develops independently of these infections. The most common co-infection was BV (58.3%).

Discussion

The median age of *M. genitalium* participants was 25 (22, 27) years and majority of the participants were African American (83.3%) and single (91.7%). Our result agrees with the demographic pattern of *M. genitalium* and other STIs as described in other studies [11,12]. Patients with STIs tend to be younger and African Americans are disproportionately affected. Oakeshott et al. [12] demonstrated young age and race as risk factors for *M. genitalium*, in addition, majority of patients in the Baltimore study were African American. Olsen et al. had a very low prevalence of *M. genitalium* among married Vietnamese women [13].

The prevalence of *M. genitalium* (8.9%) was comparable to that of *C. trachomatis* (7.8%), which was one of our hypotheses; and greater than the prevalence of gonorrhea, which was 1.8% (p=0.017). The prevalence of *M. genitalium* has been reported to range from 0% to 40% in the literature depending on the clinic/site that was sampled and the type of specimen collected (i.e., vaginal vs. cervical vs. urine samples) [14,15]. Gaydos et al. [11] reported *M. genitalium* prevalence of 19.2% in a Baltimore STD clinic; in the PEACH study, approximately 15% of women were infected with *M. genitalium*, 14% were infected with *C. trachomatis* and 15% were infected with *N. gonorrhoeae* [16]. Conversely, Oakeshott et al. [12] reported a baseline prevalence of 3.3% in the community. A national longitudinal study of adolescent health showed that genital prevalence of *M. genitalium* (approximately 1%) was approximately between those of *N. gonorrhoeae* (0.4%) and *C. trachomatis* (4.2%) [14]. When we looked at history of previous STIs, there was no significant relationship between *M. genitalium* and other STIs.

A significant observation was that subjects with lower condom use had increased probability of *M. genitalium* (p=0.037). Condom use, which would be expected to be protective against *M. genitalium* infection if sexual transmission were the main route of transmission was measured in only four studies and these, provided conflicting information. Two of these studies found no association between condom use and *M. genitalium* infection, the remaining two studies reported opposite results [17,18].

Among West African commercial sex workers, women who reported condom use with all clients had less *M. genitalium* infection when compared with women who did not use condoms all the time (24.3% vs. 33.0%, P=0.02) [19]. In contrast, among young adults in the National Longitudinal Study of Adolescent Health, condom use was associated with an increased prevalence of *M. genitalium* [14]. Although these disparate results suggest condoms may not be effective against *M. genitalium* infection, condom use data may be difficult to interpret.

There was no significant difference in presenting symptoms and no difference in the rates of PID and cervicitis among the different STIs. Our results differ from that of other studies which found an increase in cervicitis and PID among patients with *M. genitalium* infection [11,12,20]. Bjartling et al. [20] demonstrated *M. genitalium* was an independent and strong risk factor for both cervicitis and PID although compared to *C. trachomatis,* clinical manifestations were less frequent. On the other hand, our study agrees with that of Tosh et al. [21], the authors found that women identified with *M. genitalium* in a primary care center were no more symptomatic than uninfected women [21]. Manhart et al. [14] also found that lower genital tract; *M. genitalium* infection was not associated with symptoms.

Overall, 28.3% of our patients presented with abnormal vaginal discharge but there was no difference between *M. genitalium* positive and negative participants when vaginal discharge was analyzed. Results are mixed about the role of vaginal discharge in *M. genitalium* infection; some studies found no correlation between *M genitalium* and vaginal discharge while others did demonstrate a relationship. Vaginal discharge was more common in women with lower genital tract *M. genitalium* infections compared to women without *M. genitalium* among 390 minority women attending a public health clinic [22]. Vandepitte et al. [23] found that urethritis and mucopurulent vaginal discharge were associated with *M. genitalium* infection in a group at high risk for HIV and other STIs in Uganda.

Bacterial vaginosis was the most common detectable co-infection with *M. genitalium* in our study. This agrees with the UK community based study where presence of BV was a risk factor for *M. genitalium*.

Results of co-infection in *M. genitalium* studies are also mixed [11,16,24-26]. While the PEACH study and Baltimore study documented a high rate of co-infection [11,16], other studies reported little or none [24,26].

Conclusion

Mycoplasma genitalium was as prevalent as chlamydia in our study. The clinical spectrum of *M. genitalium* infection has been reported to be similar to that observed with chlamydial infection. Although not significantly associated with morbidity (cervicitis and PID) in our study, our study was limited by the number of patients who tested positive for *M. genitalium*.

Sexually transmitted infections are prevalent public health issues. In women, STI can cause PID, a significant public issue in the United States and worldwide. Adverse sequelae, including tubal factor infertility, chronic pelvic pain, recurrent PID and ectopic pregnancy can occur if PID treatment is delayed or avoided. Although PID an ascending infection is polymicrobial, *M. genitalium* has been identified as a possible etiologic agent, and our study has shown that *M. genitalium* is as prevalent as chlamydia. Due to the asymptomatic nature, like chlamydia, *M. genitalium* may go undetected, left untreated, and subsequently progress to reproductive morbidity.

Limitations

Our study is single-centered with small sample size of *M. genitalium* patients. We were unable to detect major differences in our univariate analyses.

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