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Mycoplasma genitalium infection in women attending an STI clinic: diagnostic specimen type, co-infections, and predictors

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Abstract

In female sexually transmitted infection (STI) clinic attendees, *Mycoplasma genitalium* (MG) was more frequently detected using vaginal (53/73) versus endocervical (43/73) specimens. In women without other STIs, MG detection (N=44) was associated with age≤ 22 years (odds ratio (OR) 2.53, P=0.006) and clinical evidence of cervicitis (OR 2.11, P=0.03).

Keywords

Mycoplasma genitalium; detection rate; cervicitis

Mycoplasma genitalium (MG) is an emerging sexually transmitted infection (STI) in women,[1-3] and has been associated with cervicitis[4-6], pelvic inflammatory disease (PID)[2, 6, 7] and salpingitis.[8, 9] In high-risk women attending STI clinics, the MG prevalence is between 7-26%.[10] Nucleic acid amplification tests (NAATs) have allowed MG detection for research purposes; however, the optimal genital specimen in women remains unclear. Some analyses reported the highest sensitivity for MG detection using vaginal specimens, [11, 12] whereas others observed a better performance with urine PCR.[13] Identification of the optimal specimen for MG detection in women is critical to facilitating its application in clinical practice.

MG has frequently been detected in women co-infected with other STIs, especially *Chlamydia trachomatis* (CT).[14-16] In the absence of commercially available tests for MG detection, determining the likelihood of MG co-infections in women is particularly important in the clinical management of women with evidence of persistent urogenital tract infection despite treatment for other STIs. Assessing predictors of MG infection in the absence of other STIs is also essential to unraveling the independent role of this emerging infection.

We conducted a prospective, cross-sectional study of women attending a STI clinic to: 1) compare the MG detection rate of vaginal and endocervical swab specimens using nucleic

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acid amplification tests (NAATs); 2) determine the prevalence of MG co-infection among NG, CT and TV-infected women; 3) identify predictors of MG infection in the absence of other STIs.

English-speaking women, age ≥18 years, were recruited from a public STI clinic in Durham, North Carolina between March 2007 and September 2008. All subjects provided written informed consent and the study was approved by the Biomedical Institutional Review Board of the University of North Carolina. Each participant underwent a structured history and completed a questionnaire regarding demographic and behavioral risk-factors. Vaginal swabs were collected for: 1) routine wet mount microscopy, 2) InPouch TV culture (BioMed Diagnostics) and 3) transcription-mediated amplification (TMA) testing for TV using the APTIMA TV analyte-specific reagents (TV ASR) [17], and a research TMA assay for MG (Gen-Probe, Inc.).[15] Endocervical swabs were obtained for: 1) Gram stain and 2) CT, *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV) and MG TMA testing. The FDA-cleared APTIMA Combo2 test was used for NG and CT detection according to the manufacturer's instructions (Gen-Probe, Inc.).

Cervicitis was defined clinically as the presence of purulent, mucopurulent or yellow endocervical discharge or endocervical friability on speculum exam. MG-positive women who were negative for NG, CT and TV-infections were defined as being infected with MG-only. Women were considered asymptomatic if they reported the absence of vaginal discharge, vaginal irritation, dysuria, genital itching, lower abdominal pain, genital ulcers or rashes. Vaginal discharge was clinically defined as the presence of any non-clear discharge on speculum exam. Bacterial vaginosis (BV) was diagnosed clinically using Amsel's Criteria.[18]

Using an infected-patient standard (IPS), we defined MG positivity as a positive vaginal and/or endocervical TMA assay. The detection rate of vaginal and endocervical specimens were determined relative to the IPS-positive patients and Cohen's kappa statistic (κ) was used to evaluate the agreement between the two specimens for MG detection.

The MG, NG, CT and TV prevalence was determined using the number of positive results among all women tested for that pathogen. The prevalence of MG co-infections was calculated using the number detected with MG among women already identified with NG, CT, or TV infections. Pearson's chi-squared test was used to assess for associations between MG-only detection and patient demographic and clinical variables compared to that in women without detected STIs. Variables associated with MG-only at a $P<0.1$ in bivariable analysis were included in multivariable logistic regression models to calculate adjusted odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were performed with Stata/IC version 11 (Stata Corp, College Station, TX).

We enrolled 381 women in this study, of which 89% were of black race/ethnicity; the median age was 26 (interquartile range [IQR]: 21-35). Eighty percent of women reported at least one symptom, with vaginal discharge being the most common (54%).

Overall, the prevalence of MG was 19.2% (73/381), compared to 26.5% for TV, 12.6% for CT and 6.0% for NG. MG co-infections were detected in 30.4% of women with NG, 25.0% with CT and 19.8% with TV infections. Among women without other STIs, the prevalence of MG was 11.5% (44/381).

Of the 73 IPS-positive women, 53 (72.6%) were detected by vaginal specimens and 43 (58.9%) by endocervical specimens, (Table 1). MG was detected by both genital specimens in 23/73 (32%) women, resulting in low to moderate agreement between the specimens (κ=0.41). In comparison, very good agreement (κ=0.92) was observed between vaginal and

endocervical specimens for TV detection, suggesting that the low agreement between specimens for MG detection was not attributable to collection techniques.

In bivariable analyses comparing women with MG-only to those without detectable STIs, MG was positively associated with age ≤22 years (P=0.001), being asymptomatic (P=0.02) and cervicitis (P=0.03), and negatively associated with reported vaginal discharge (P=0.03) and douching (P=0.02), (Table 2). In multivariable analysis, age ≤22 years (OR 2.53, 95% CI 1.25-5.12) and cervicitis (OR 2.11, 95% CI 1.04-4.26) remained associated with MG-only detection. In multivariable analyses of each specimen type, age ≤22 years was associated with endocervical (N=12, OR 6.91, 95% CI 1.65-28.9) but not vaginal (N=20, OR 2.16, 95% CI 0.79-5.93) detection of MG-only. A trend was observed for an association between cervicitis and MG-only detection by endocervical (OR 2.56, 95% CI 0.67-9.76) and vaginal specimens (OR 1.93, 95% CI 0.72-5.20), although the estimates were imprecise given the small numbers of patients in each group.

In our study population, MG was detected more frequently than both NG and CT, and was commonly isolated in women with other STIs. A higher prevalence of MG relative to CT has been observed by other investigators, [6, 15, 16] and lower estimates reported in other studies may reflect regional differences in MG prevalence.

The vaginal swab specimen had a higher detection rate for MG than the endocervical swab specimen. Although we were limited by not having an independent comparator assay with which to determine the sensitivity of the genital specimens, our MG TMA research assay is likely to be more sensitive than DNA-based PCR methods as it targets rRNA which is present in the cell in multiple copies as opposed to single-copy genes.[12] The higher detection rate observed using vaginal versus endocervical specimens supports the findings of other investigators.[11, 12, 16] This may reflect minimal host immune response to MG infection in the vaginal epithelium, and thus greater bacterial survival in the vagina compared to the endocervix, where the inflammatory response to MG by endocervical epithelial cells is more robust.[19] This may also explain reported associations between MG and cervicitis,[3-5] but not vaginitis.[20]

Although more cases of MG were detected using vaginal specimens, more than a quarter of MG-positive women would have been missed using either specimen type alone. Lillis et al. reported relative sensitivities for vaginal and endocervical specimens of 85.7% and 74.3%, respectively using a PCR assay, which increased to >95% when the results of the two specimens were combined.[11] However, testing from multiple specimens is not feasible in resource-limited settings such as public STI clinics. Self-collected vaginal swabs are preferred by women and have higher sensitivities for STI detection than more invasive forms of specimen collection.[12, 21-23] Therefore, the testing of a single self-collected vaginal swab for NG, CT, TV and MG may result in the most cost-effective screening recommendation; however, the performance of self-collected vaginal specimens for MG detection remains to be determined.

In MG-positive women without other co-infections, young age and cervicitis were the only patient characteristics associated with MG detection. Being asymptomatic was associated with a 2-fold increased risk of detecting MG-only, but was only significant in bivariable analyses; this finding which has been noted by others[24] suggests that MG infections in women may not be associated with specific urogenital symptoms. The association between young age and MG detection has been previously observed [25-27] and is likely mediated by both biological (i.e. endocervical ectopy) and behavioral (i.e. number of sexual partners and inconsistent condom use) risk factors.[28, 29] The association between MG and cervicitis has

been reported by some investigators [3-6] but not others, [14, 15, 30] which likely stem from the wide discrepancy in how cervicitis is defined.

In conclusion, NAATs using vaginal specimens for MG detection provide higher detection rates than endocervical specimens, but would still miss a fourth of infections that we identified using an IPS. Women with CT, NG and TV-infections have a high prevalence of MG co-infection; however, MG prevalence is also high at 11.5% among women without other STIs. Young age and cervicitis were the only predictors significantly associated with MG-only infection in our study, and we found no associations with urogenital symptoms. Therefore, if NAATs for MG detection become commercially available, clinicians should consider screening young asymptomatic women with cervicitis but recognize the potential limitations of the assay.

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