REVIEW ARTICLE

Mycoplasma genitalium Infection and Female Reproductive Tract Disease: A Meta-analysis

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To determine the association between *Mycoplasma genitalium* infection and female reproductive tract syndromes through meta-analysis, English-language, peer-reviewed studies were identified via PubMed, Embase, Biosis, Cochrane Library, and reference review. Two reviewers independently extracted data. Random-effects models were employed to calculate summary estimates, between-study heterogeneity was evaluated using I^2 statistics, publication bias was assessed via funnel plots and the Begg and Egger tests, and methodologic quality was rated. *Mycoplasma genitalium* infection was significantly associated with increased risk of cervicitis (pooled odds ratio [OR], 1.66 [95% confidence interval {CI}, 1.35–2.04]), pelvic inflammatory disease (pooled OR, 2.14 [95% CI, 1.31–3.49]), preterm birth (pooled OR, 1.89 [95% CI, 1.25–2.85]), and spontaneous abortion (pooled OR, 1.82 [95% CI, 1.10–3.03]). Risk of infertility was similarly elevated (pooled OR, 2.43 [95% CI, .93–6.34]). In subanalyses accounting for coinfections, all associations were stronger and statistically significant. Testing of high-risk symptomatic women for *M. genitalium* may be warranted.

Keywords. *Mycoplasma genitalium*; cervicitis; pelvic inflammatory disease; pregnancy outcomes; female infertility.

Mycoplasma genitalium has been considered an emerging sexually transmitted infection (STI) for the past 5–10 years, and its association with nongonococcal urethritis in men is well established, with a pooled odds ratio (OR) of 5.5 (95% confidence interval [CI], 4.3–7.0) [1]. However, associations with female cervicitis, pelvic inflammatory disease (PID), infertility, and preterm delivery have been inconsistent [1]; fewer studies have been conducted in women, and sample sizes have been small. Although several reviews of the association of *M. genitalium* with female genital tract disease have been published, none has quantitatively evaluated the full spectrum of female reproductive tract syndromes [1, 2], and uncertainty over the public health importance of this organism remains. In many settings, *M. genitalium* responds poorly to standard therapies [3, 4], and evidence that it plays a role in reproductive tract disease would have substantial implications for current treatment recommendations.

To comprehensively evaluate the role of *M. genitalium* infection in women, we conducted meta-analyses of studies published since 1980 on the association with cervicitis, PID, adverse pregnancy outcomes, and female infertility, assessing each separately. We evaluated heterogeneity among studies, potential publication bias, and study quality. Where the number of studies allowed, we evaluated whether associations varied by geographic region, method of detecting *M. genitalium*, and definition of the outcome, through stratified analyses. Subanalyses evaluated studies that accounted for coinfections with other known pathogens.

METHODS

Data Sources and Searches

We searched the literature to identify studies published from 1 January 1980 through 25 June 2014 by using

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computerized databases (PubMed, Embase, Biosis, Cochrane Library) and scrutinizing references of identified articles. The following search terms were employed in Medical Subject Heading terms and all fields (See Supplementary Appendix A for full search details): (1) mycoplasma genitalium AND cervicitis, (2) mycoplasma genitalium AND infertility, (3) mycoplasma genitalium AND (pregnancy OR pregnancy complications OR pregnancy outcomes), (4) mycoplasma genitalium AND (pelvic inflammatory disease OR PID OR pelvic infection).

Study Selection

Using preestablished criteria, studies were included if they (1) reported data from an original peer-reviewed study; (2) employed a cross-sectional, cohort, or case-control design; (3) provided adequate description of the assay used; (4) defined the outcome with sufficient detail to evaluate comparability with other studies; (5) reported sufficient data to determine the association with reproductive tract syndromes; and (6) were published in English. Studies were excluded if they reported on the development of laboratory assays, studied genomics, constituted case series or animal studies, had no comparison group, or reported only prevalence. Clinical guidelines, editorials, and letters were also excluded, as well as conference abstracts given their preliminary nature and limited information about study design. For studies from overlapping populations, the study with the largest sample size and most complete analysis was selected. Databases were queried throughout the meta-analysis to ensure complete coverage of current literature.

Data Extraction and Quality Assessment

Using a standardized form, 2 reviewers (R. L. and L. E. M.) simultaneously extracted the following data items: author, year, study location, study design, study population, sample size, detection method for *M. genitalium*, outcome definition, crude effect estimate, and adjusted effect estimate (if available). If crude effect estimates were not presented, they were calculated by the investigative team. If estimates could not be calculated from available data, authors were contacted for additional information. If estimates were provided for multiple definitions of the outcome, objective definitions (eg, polymorphonuclear leukocyte [PMN] counts, laparoscopy) were prioritized over clinical diagnoses. If multiple objective definitions were presented, estimates based on the most rigorous definition (eg, highest PMN counts) were selected. Discrepancies were discussed between the 2 reviewers to reach consensus.

To evaluate the quality of included studies, we adopted the Cochrane Collaboration's domain-based approach for randomized controlled trials [5]. Although numerous rating scales have been developed to evaluate the quality of observational studies, most score individual components and combine them to create an overall score. This involves inherent weighting of components, some of which may not directly affect the validity of the study [6]. Therefore, we individually assessed the following domains of potential bias: source population, method of participant selection, rigor of the exposure measurement, rigor of the outcome measure, control for confounding, and whether the reported data were from a primary analysis. We assigned a rating of poor, fair, or good for each of these criteria based on expert knowledge of the topic area and study methods. We then assigned studies an overall quality rating of "good" if no more than 2 of the above criteria were deemed fair; "fair" if ≥3 of the criteria were deemed fair; and "poor" if ≥2 of the criteria were deemed poor (see Supplementary Appendix B for a summary of the full rating scheme). Quality ratings were tied to a specific outcome and do not necessarily reflect the intrinsic quality of the study: in some cases, the same study received different quality ratings when it was included in >1 analysis.

Data Synthesis and Analysis

Data were aggregated across studies for each syndrome to determine an overall summary OR using random-effects models. Studies with a zero cell were included by adding 0.5 to all cell counts to permit calculation of an effect estimate and 95% CI [7]. All models were executed first using crude estimates only and subsequently using adjusted estimates where provided. In all cases, these models did not differ materially, and we present data from the model incorporating the adjusted estimate where provided and crude estimates for studies where adjusted estimates were not provided. Subanalyses restricted to studies that accounted for coinfections (ie, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*) were conducted for each outcome.

We used the I^2 statistic to assess heterogeneity: <25% was deemed low and >75% was deemed considerable [8]. Funnel plots were created to visually assess possible publication bias. We also performed the Begg adjusted rank correlation test, a numerical analogue to the funnel plot [9], and the Egger regression asymmetry test to account for the potentially lower power of the Begg test [10]. All analyses were conducted using Stata software version 13.1. Institutional review board approval was not required for these analyses of the published literature, and there was no external funding.

RESULTS

The systematic search for studies of *M. genitalium* and female reproductive tract syndromes returned 1080 titles. Of these, 311 evaluated cervicitis, 292 studied PID, 174 summarized adverse pregnancy outcomes, and 203 assessed infertility.

M. genitalium and Cervicitis

After excluding duplicate citations, 174 potentially eligible studies were identified (Supplementary Appendix Figure 1). Of these, 151 were excluded after review of title, abstract, and

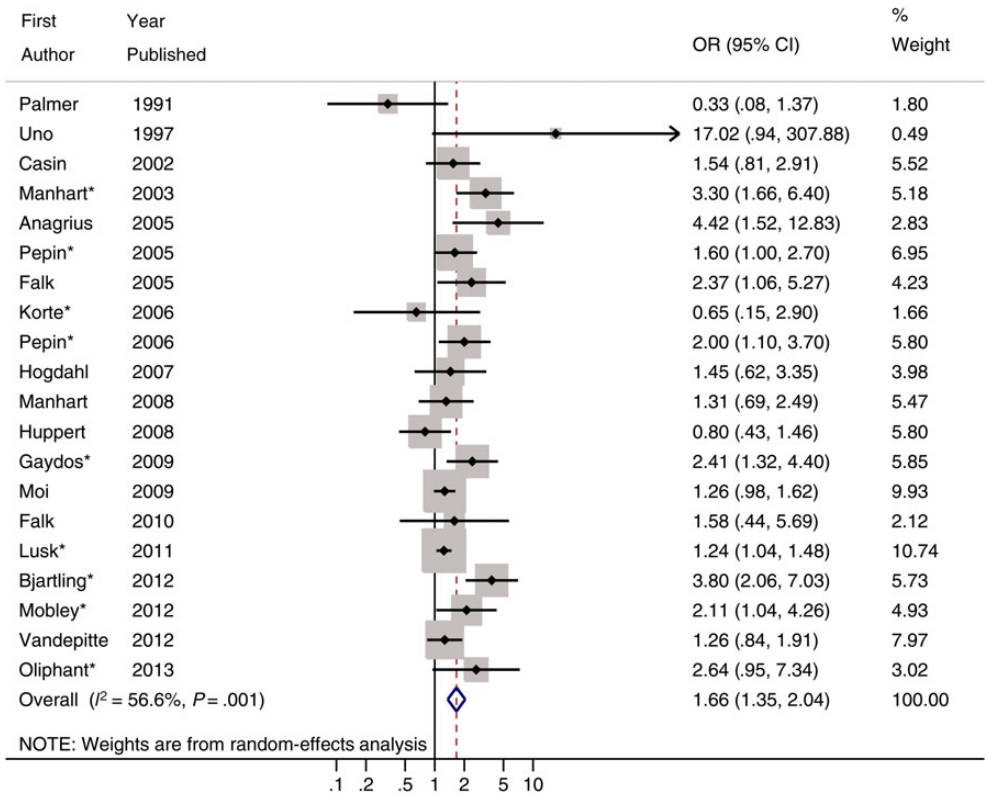

Figure 1. Forest plot of the association between *Mycoplasma genitalium* and cervicitis. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.

publication language. Upon full text review, 3 additional studies were excluded [11–13]. The 20 included studies evaluating the association between cervicitis and *M. genitalium* are summarized in Supplementary Appendix Table 1. Only 9 studies provided adjusted effect estimates [14–22]. Most used in-house polymerase chain reaction (PCR) assays to detect *M. genitalium*, although 2 studies employed the APTIMA transcription-mediated amplification (TMA) assay [21, 23] (Hologic, San Diego, California) and 1 study used both TMA and PCR [18]. Most studies employed an objective definition of cervicitis (≥10 to ≥30 PMNs in cervical exudates) with or without clinical criteria, but 6 studies relied solely on a clinical definition [15, 16, 18, 21, 23, 24]. Quality ratings were "good" for 9 [14, 15, 17–19, 22, 24–26] and "fair" for 11 [16, 20, 21, 23, 27–33] studies (Supplementary Appendix Table 5).

In the meta-analysis of cervicitis, *M. genitalium* infection was associated with a significantly increased risk of cervicitis, with a pooled OR of 1.66 (95% CI, 1.35–2.04) (Figure 1). There was moderate between-study heterogeneity (I^2 = 56.6% [95% CI, 28.4%–73.6%]), but no significant publication bias (Begg P = .299; Egger P = .54) (Supplementary Appendix Figure 2). In stratified analyses, there was no substantial difference in the pooled effect estimate or the I^2 statistic by geographic location of the study, study design, type of assay, or definition of cervicitis (data not shown). In subanalyses of studies that accounted for coinfections [14–21], the pooled OR was 1.99 (95% CI, 1.39–2.84) with moderate between-study heterogeneity (I^2 = 70.7% [95% CI, 39.4%–85.9%]).

M. genitalium and PID

After excluding duplicate citations, 175 potentially eligible studies were identified (Supplementary Appendix Figure 3). One hundred fifty-eight references were excluded based on title and abstract review, and an additional 7 studies were excluded following full text review [34–40], resulting in 10 studies with data on the association between *M. genitalium* and PID (Supplementary Appendix Table 2). Adjusted effect estimates were presented for only 4 studies [20, 41–43]. Seven studies detected *M. genitalium* infection using PCR, 2 studies used serology [41, 44], and 1 combined PCR and serology [45]. The majority employed clinical diagnoses of PID, whereas 4 studies used objective definitions of endometritis [42, 46] and salpingitis [44, 45] determined by biopsy or laparoscopy (with or without clinical diagnoses). Quality for of the studies was rated "good" for 4 studies [24, 42, 43, 46] and "fair" for 6 [20, 41, 44, 45, 47, 48] (Supplementary Appendix Table 5).

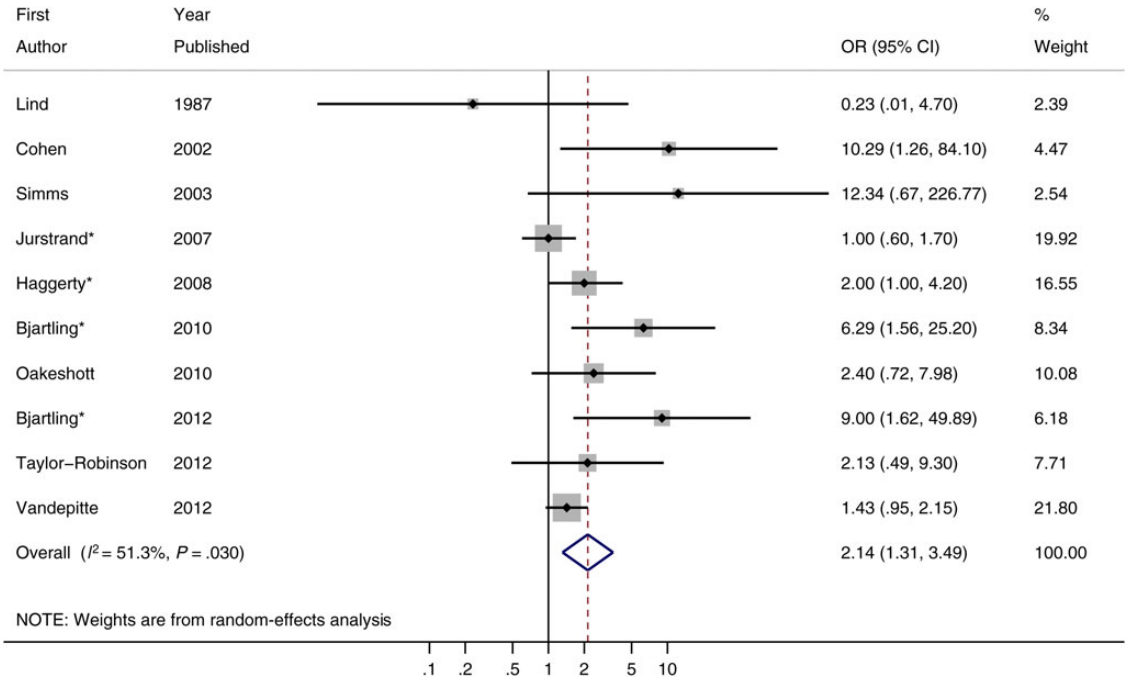

Figure 2. Forest plot of the association between *Mycoplasma genitalium* and pelvic inflammatory disease. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.

In the meta-analysis of PID, *M. genitalium* infection was associated with significantly increased risk of PID, with a pooled OR of 2.14 (95% CI, 1.31–3.49) (Figure 2). There was moderate between-study heterogeneity (I^2 = 51.3% [95% CI, .0%–76.3%]) but no significant publication bias (Begg P = .98; Egger P = .055) (Supplementary Appendix Figure 4). Excluding studies that used serology, the pooled OR was 2.73 (95% CI, 1.60–4.66) (Supplementary Appendix Figure 5) with moderate between-study heterogeneity (I^2 = 42.2% [95% CI, .0%–74.4%]). Among studies that accounted for coinfections [20, 41–43], the pooled OR was 2.53 (95% CI, 1.03–6.26) with moderate between-study heterogeneity (I^2 = 73.0% [95% CI, 24.0%–90.4%]).

M. genitalium and Adverse Pregnancy Outcomes

After excluding duplicate citations, there were 95 potentially eligible references (Supplementary Appendix Figure 6), 82 of which were excluded after review of title, abstract, or publication language. Four additional studies were excluded following full text review [49–52]. Although 10 studies met inclusion criteria (Supplementary Appendix Table 3), only 9 were included in the meta-analysis; 1 study assessing ectopic pregnancy was evaluated separately [41]. Six studies presented information on preterm birth [53–58], 3 presented data on spontaneous abortion [14, 38, 59], and 2 presented data on the association between *M. genitalium* and stillbirth [56, 59]. All adverse pregnancy outcomes were defined clinically, and only 3 studies reported adjusted effect estimates [38, 54, 59]. One study used TMA [54] to detect *M. genitalium*, whereas all others used PCR. Eight studies were assigned "good" quality ratings [38, 41, 54–59], and 2 were designated "fair" [14, 53] (Supplementary Appendix Table 5).

In the meta-analysis of preterm birth, *M. genitalium* infection was significantly associated with increased risk of preterm birth, with a pooled OR of 1.89 (95% CI, 1.25–2.85) (Figure 3). Between-study heterogeneity was low (I^2 = 0.0% [95% CI, .0%–44.5%]), and there was no significant publication bias (Begg P = .85; Egger P = .74) (Supplementary Appendix Figure 7). Among studies accounting for coinfections [54, 58], the pooled OR was 2.33 (95% CI, 1.08–5.01), and between-study heterogeneity remained low (I^2 = 0.0% [95% CI, .0%–.0%]).

In the meta-analysis of spontaneous abortion, *M. genitalium* infection was significantly associated with increased risk of spontaneous abortion, with a pooled OR of 1.82 (95% CI, 1.10–3.03) (Figure 4). There was low between-study heterogeneity (I^2 = 0.0% [95% CI, .0%–82.2%]) and no significant publication bias (Begg P = .60; Egger P = .26) (Supplementary Appendix Figure 8). Only 1 study adjusted for coinfections [59], precluding subanalysis.

A single case-control study on ectopic pregnancy [41] used serology and reported no association (OR, 1.0 [95% CI, .5–2.0]). The 2 studies with data on stillbirth used PCR and demonstrated no statistically significant associations, with ORs of 1.07 (95% CI, .42–2.42) [56] and 1.36 (95% CI, .76–2.45) [59], but were too few to pool.

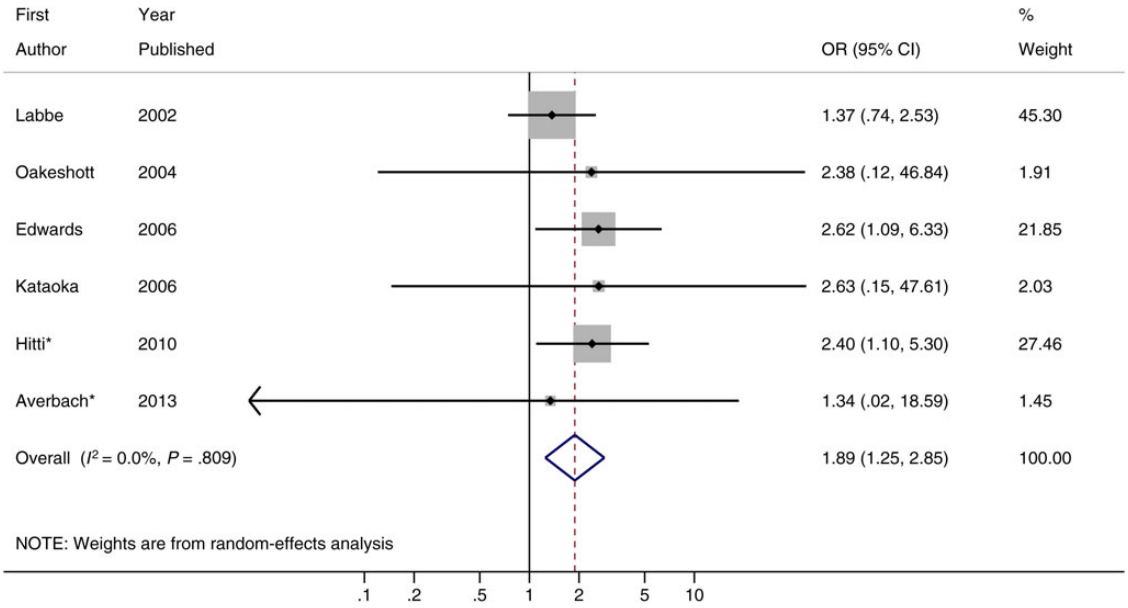

Figure 3. Forest plot of the association between *Mycoplasma genitalium* and preterm birth. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.

M. genitalium and Female Infertility

After excluding duplicate citations, 112 potentially eligible studies were identified (Supplementary Appendix Figure 9). One hundred two references were excluded based on title and abstract, and an additional 3 studies were excluded following full text review [34, 60, 61], resulting in 5 studies evaluating the association between *M. genitalium* and female infertility (Supplementary Appendix Table 4). Adjusted effect estimates were reported in 3 studies [42, 62, 63]. Most studies evaluated women attending fertility clinics, comparing confirmed tubal factor infertility to other causes of infertility identified through laparoscopy, culdoscopy, or hysterosalpingography [62–65]. A

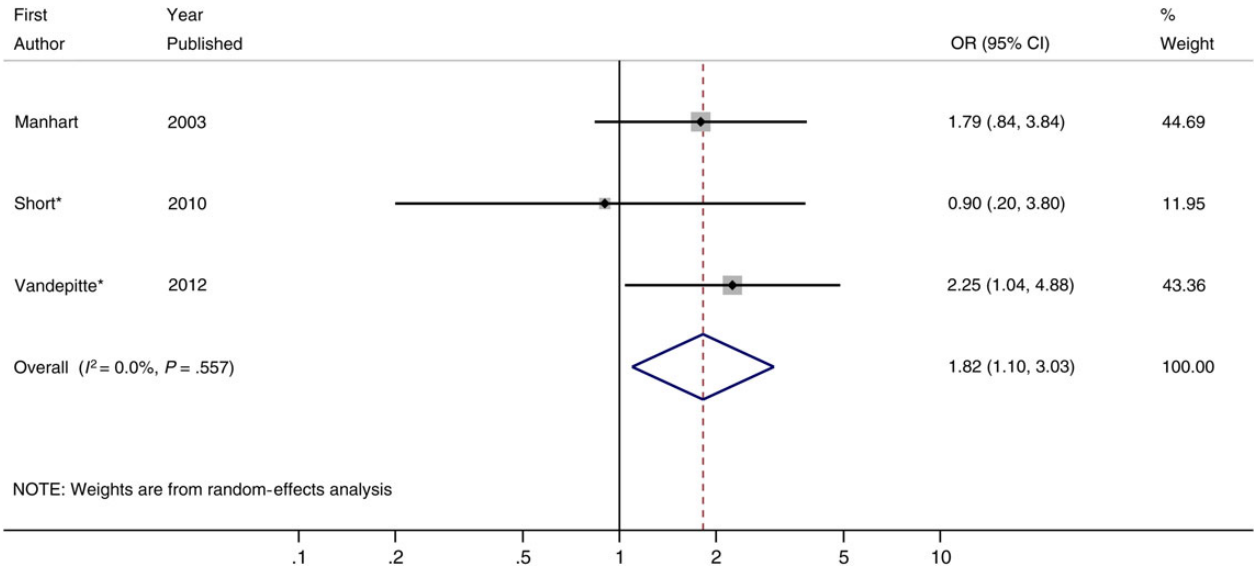

Figure 4. Forest plot of the association between *Mycoplasma genitalium* and spontaneous abortion. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.

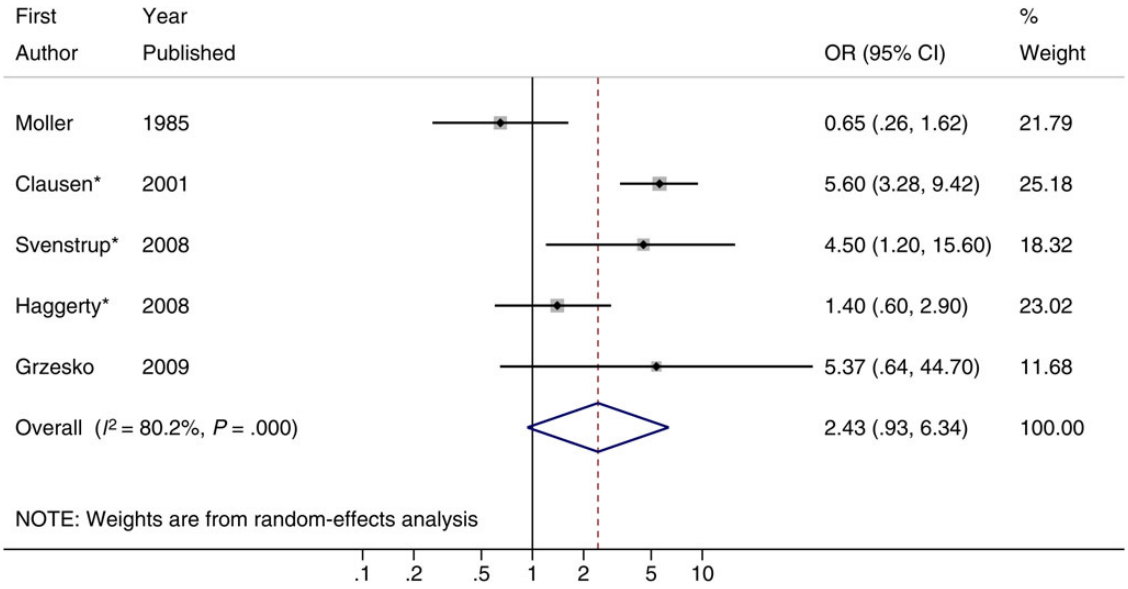

Figure 5. Forest plot of the association between *Mycoplasma genitalium* and female infertility. *Adjusted effect estimate (crude effect estimate in all other cases). Abbreviations: CI, confidence interval; OR, odds ratio.

single study evaluated women with clinically diagnosed PID and defined infertility by self-report [42]. Another compared women with infertility from all causes (including male infertility) to women with proven fertility [65]. Three studies used serology [62–64] and 2 used PCR [42, 65]. "Good" quality ratings were assigned to 3 studies [42, 62, 63], and 2 were designated as "fair" [64, 65] (Supplementary Appendix Table 5).

In the meta-analysis of infertility, the pooled OR was 2.43 (95% CI, .93–6.34) (Figure 5). There was considerable between-study heterogeneity (I^2 = 80.2% [95% CI, 53.5%–91.6%]), but no significant publication bias (Begg P = .62; Egger P = .70) (Supplementary Appendix Figure 10). Among studies accounting for coinfections [42, 62, 63], the pooled OR was 3.27 (95% CI, 1.25–8.57), with considerable between-study heterogeneity (I^2 = 75.9% [95% CI, 20.8%–92.7%]).

DISCUSSION

These meta-analyses of the published literature on the association between *M. genitalium* and female reproductive tract disease produced remarkably consistent findings, demonstrating an approximately 2-fold increase in risk for cervicitis, PID, spontaneous abortion, preterm birth, and infertility. With the exception of analyses of infertility, these pooled estimates were all statistically significant. Subanalyses of studies that accounted for other known pathogens demonstrated greater pooled estimates for all 5 syndromes, all of which were statistically significant, providing strong evidence of an association.

Only the association between *M. genitalium* and cervicitis had been previously assessed in meta-analysis, and our pooled estimate of 1.7 was similar to the initial pooled estimate of 2.2 (95% CI, 1.6–2.9), also from random-effects modeling [1]. This similarity was despite our exclusion of 2 studies in the earlier meta-analysis [43, 66] and the addition of 8 new studies [16, 19–22, 24, 27, 32]. The consistency of results across definitions of cervicitis and methods of detection further suggests that *M. genitalium* plays a role in cervicitis. Despite this association, cervicitis is typically asymptomatic, and diagnosis and treatment are recommended primarily to interrupt transmission and to prevent pathogens from ascending to the upper reproductive tract and causing PID [67].

PID causes significant morbidity and, left untreated, can result in infertility, ectopic pregnancy, and chronic pelvic pain [68]. Costs associated with acute PID episodes range from approximately $700 to $8480 per episode for outpatient and inpatient care, respectively [69], and indirect costs related to sequelae are far higher, highlighting the need for rapid and appropriate treatment. Our finding of a significant association between *M. genitalium* and PID has implications for currently recommended therapies [70], which specify the use of antibiotics with poor efficacy against *M. genitalium*. Observations from the PID Evaluation And Clinical Health trial, where 56% of *M. genitalium*–infected women with PID experienced persistent endometritis after standard therapy [42], highlight the inadequacy of these regimens. Nevertheless, the proportion of PID cases due to *M. genitalium* remains unknown, and forthcoming

updates to the Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines recommend that standard antimicrobial therapy not be altered unless PID persists and *M. genitalium* is identified [70].

Preterm delivery of an infant has numerous causes [71], and infectious agents contribute only a small proportion. Therefore, it was remarkable that we observed a 2-fold increase in risk for preterm birth and spontaneous abortion associated with *M. genitalium* infection, greater than the risk associated with *T. vaginalis* in a recent meta-analysis (pooled relative risk, 1.42 [95% CI, 1.15–1.75]) [72]. Nevertheless, the prevalence of this organism in low-risk populations is generally low (approximately 2.0%) [2, 73], suggesting that universal testing of pregnant women for *M. genitalium* is not warranted. Screening high-risk pregnant women (eg, women with multiple partners or previous STIs) may be warranted, but further studies to determine if treating *M. genitalium* reduces risk for preterm birth will be required prior to instituting recommendations.

Infertility afflicts approximately 11% of women aged 15–44 in the United States [74], and identifying preventable causes is a priority. Although the nearly 2.5-fold increased risk of infertility associated with *M. genitalium* was the sole estimate that was not statistically significant, it was also the sole analysis with substantial heterogeneity. The stronger and statistically significant summary OR in subanalyses accounting for other known pathogens suggests a causal link with infertility. However, more sensitive and specific seroassays and longitudinal studies will be required before the association between *M. genitalium* and infertility can be definitively determined.

Treatment of *M. genitalium* infections is challenging and hampered both by the lack of a US Food and Drug Administration (FDA)–approved assay and low cure rates after syndromic therapy. Eradication of *M. genitalium* after doxycycline occurs in only approximately 30% of cases, cell wall–mediated antibiotics are ineffective, and azithromycin resistance is increasing [4, 75, 76]. Moxifloxacin is recommended in cases of azithromycin failure [70], but should be used judiciously. Ideally, targeted testing of high-risk symptomatic women would guide therapy, but until recently only in-house PCR and research-use-only assays have been available in the United States. However, the Aptima TMA assay for *M. genitalium* is highly sensitive and specific [77, 78] and is now commercially available as analyte-specific reagents [79], and a clinical trial is planned to support a 510(k) application to the FDA (D. Getman, written personal communication).

A major strength of these meta-analyses was our ability to summarize studies with varying exposure and outcome measurements. Despite this variety, heterogeneity was moderate to low in all but 1 analysis. The pooled ORs from subanalyses of studies that accounted for other pathogens were of greater magnitude and all were statistically significant, lending further confidence to the conclusion that *M. genitalium* is causally related.

Nevertheless, there were also limitations. The number of studies on stillbirth and ectopic pregnancy was too small to draw conclusions. We used random-effects rather than fixed-effects models, erring on the side of more conservative analyses. In an inclusive approach, we retained nearly all studies in the primary analyses, potentially diluting effect estimates. Our exclusion of conference abstracts and non-English-language studies omitted some of the evidence, and 2 recent conference abstracts reported 2-fold [80] to 4-fold [81] higher risks for PID in women with *M. genitalium*; our pooled estimate may be particularly conservative.

These meta-analyses demonstrate an approximately 2-fold increased risk of cervicitis, preterm birth, spontaneous abortion, PID, and infertility in women infected with *M. gentialium*, providing strong evidence in support of a causal role. The severity and high costs associated with these conditions, as well as the limitations of syndromic therapies for *M. genitalium* infection, suggest that targeted testing of high-risk symptomatic women may be warranted. The increasing availability of diagnostic tests for *M. genitalium* will make this possible.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. R. L. and L. E. M. had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: R. L., L. E. M. Analysis and interpretation of the data: R. L., A. R.-R., L. E. M. Drafting of the article: R. L., L. E. M. Critical revision of the article for important intellectual content: R. L., A. R.-R., L. E. M. Final approval of the article: R. L., A. R.-R., L. E. M. Statistical expertise: R. L. Collection and assembly of data: R. L., L. E. M.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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