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

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Abstract

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A Meta-Analysis

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Objective: Determine the association between *Mycoplasma genitalium* and female reproductive tract disease through meta-analysis.

Methods: English-language literature published January 1, 1980-May 19, 2014 was searched, relevant studies were assessed for quality, and data on associations with reproductive tract disease abstracted. Random effects models generated pooled estimates. Heterogeneity was evaluated with the I^2-statistic; publication bias was assessed using Begg and Egger tests.

Results: A significant association was found between *M. genitalium* and cervicitis (pooled effect ratio 1.69 (95% CI 1.36-2.10)), preterm birth/spontaneous abortion (pooled OR 1.90 (95% CI: 1.38-2.60)), and pelvic inflammatory disease (pooled OR 2.14 (95% CI: 1.31-3.49)). A non-significant association was found with infertility (pooled OR 2.43 (95% CI: 0.93-6.34)), which increased in magnitude and significance after excluding an outlying study. There was low/moderate heterogeneity in all analyses and no significant publication bias.

Conclusions: *M. genitalium* was associated with adverse reproductive outcomes. Screening high-risk women may be warranted.

INTRODUCTION

Mycoplasmas are characterized by their small size and lack of cell wall and several species are pathogenic in humans. Following its isolation from the male urethra in 1980, *M. genitalium* infection was linked to several reproductive tract syndromes in men and women including urethritis, cervicitis, and possibly pelvic inflammatory disease (PID), as well as infertility, and pre-term delivery [1]. Globally, in low-risk female populations (those not attending STI or fertility clinics) the average prevalence is approximately 2.0%, similar to the overall prevalence of *Chlamydia trachomatis* in women in the United States (2.5%) [2, 3]. In high-risk women, the average prevalence of *M. genitalium* infection is substantially higher (7.3%), but ranges from 0% to 42%, depending on the setting [2]. Although the association between *M. genitalium* infection and nongonococcal urethritis (NGU) in men is well established, the association with female reproductive tract disease is less clear [1].

Annually, in the United States, sexually transmitted infections (STIs) result in over $16 billion in direct healthcare costs, with the highest burden borne by younger individuals [3, 4]. In most women, sexually transmitted pathogens first establish infection in the vagina or cervix, paving the way for ascension to the upper reproductive tract and risk for PID. Although no recent cost data are available, estimates from 1990 suggested that the direct and indirect cost of PID and PID-associated ectopic pregnancy and infertility was $4.2 billion and would reach $10 billion by 2000 [5]. Given these costs, screening and treatment programs have been developed for *Chlamydia trachomatis* and *Neisseria gonorrhoeae;* organisms clearly linked to PID. *Mycoplasma genitalium* is a recently emerging STI, and there are no estimates of the direct and indirect cost due to infection and sequelae. However, even if only a portion of PID is caused by

M. genitalium, infection with this organism would result in substantial direct and indirect cost globally.

Meta-analysis is a commonly used technique to pool information from several studies to provide a summary estimate of the association of interest. It is a particularly useful tool for combining studies with small populations, similar study designs and outcomes, and studies with lower power. Meta-analysis also provides a systematic approach to summarizing available literature that includes standardized criteria for identifying and selecting information from studies that prevents selective inclusion and subjective weighting of studies.

A systematic review and meta-analysis, assessing the association between *M. genitalium* infection and NGU in men and cervicitis in women was published in 2011[1]. This review evaluated studies published from 1997-2009, but did not generate pooled estimates for female upper reproductive tract infections (infections of the uterus, ovaries, or fallopian tubes such as PID, infertility, and adverse pregnancy outcomes) [1]. Another review, published in 2011, summarized the literature studying the association between *M. genitalium* infection and female reproductive tract infections, but a formal meta-analysis was not conducted [2]. Since the publication of these reviews, several recent studies on the possible association between *M. genitalium* and female reproductive tract infections have been published, making an up-to-date meta-analysis of this information merited.

We conducted a meta-analysis of studies published between 1980 and the present on the association between *M. genitalium* infection and female reproductive tract disease, namely cervicitis, female infertility, adverse pregnancy outcomes, and PID. Since the pathogenesis of these conditions is sufficiently different, we assessed each of them separately. We also assessed to what extent heterogeneity was present among the studies included in these analyses and to

what extent publication bias may have impacted our conclusions. Where the number of studies allowed, we assessed whether the association between *M. genitalium* infection and these female reproductive tract disease outcomes varied by geographic region or method of detection (nucleic acid amplification test (NAAT) vs. serology) of *M. genitalium*, through stratified analysis.

METHODS

To assess the relationship between *M. genitalium* infection and female reproductive tract disease, we conducted one meta-analysis for each of the female reproductive tract disease syndromes for a total of four meta-analyses. The primary exposure was detection of *M. genitalium* determined through nucleic acid amplification test (NAAT), serology, or culture. The four outcomes of interest were cervicitis, adverse pregnancy outcomes, female infertility, and pelvic inflammatory disease (PID).

Search Strategy: This meta-analysis included published studies from January 1, 1980 through May 19, 2014. Studies were identified through a multi-faceted approached: 1) A computerized search of relevant databases including PubMed, Embase, Biosis, Cochrane Library, 2) scrutinizing the references of the identified papers for additional sources, and 3) contact with field experts for any additional references. Searches of computerized literature were conducted using the following search strategies for each meta-analysis: (See Appendix A for Full Search details) 1) ***M. genitalium*** **and Cervicitis:** 'mycoplasma genitalium AND cervicitis' in MeSH terms and all fields, 2) ***M. genitalium*** **and Infertility:** 'mycoplasma genitalium AND infertility' in MeSH terms and all fields, 3) ***M. genitalium*** **and Pregnancy Outcomes:** 'mycoplasma genitalium AND (pregnancy OR pregnancy complications OR pregnancy outcomes)' in MeSH

terms and all fields, 4) ***M. genitalium* and PID:** 'mycoplasma genitalium AND (pelvic inflammatory disease OR PID OR pelvic infection)' in MeSH terms and all fields.

Inclusion and Exclusion Criteria: Studies were included if they met the following criteria: 1) The authors reported data from an original peer-reviewed study, 2) the study employed a cross-sectional, cohort, or case-control design, 3) the study provided adequate description of the assay used to detect *M. genitalium* and sufficient data to determine the association between *M. genitalium* and reproductive tract syndromes, and 4) the study was published in English. Many of these outcomes are clinically defined or not standardly defined; therefore published articles used varying definitions for their outcomes. All definitions of the outcome were included in the search criteria and articles were selected for inclusion if they had defined their exposure and outcome measurement with sufficient detail to evaluate comparability with other studies. Studies were excluded if they reported only on the development of laboratory assays, or were studies of genomics, case series or animal studies, had no comparison group, or reported only on prevalence. Articles were also excluded if they reported on clinical guidelines or were conference abstracts or editorials/letters. If there were overlapping studies from the same population, the study with the most complete population size and analysis was chosen for inclusion. Databases were queried several times throughout the meta-analysis study to ensure complete coverage of current literature.

Data Abstraction and Review: All relevant data were extracted simultaneously by two reviewers (RL and LEM) using a standardized data collection form. Discrepancies were discussed between the two reviewers and a consensus on inclusion and data elements was reached. Data were

collected for the following items: first author, year, study location, study design, study population, sample size, method used to detect *M. genitalium*, definition of the outcome, crude effect estimate, and adjusted effect estimate (if available, including covariates). If crude effect estimates were not presented in the study, estimates were calculated by the investigation team and provided in summary tables. If crude effect estimates could not be calculated from the available data, authors were contacted to provide additional information. If estimates were provided for multiple definitions of the outcome, objective definitions (e.g. PMN counts, laparoscopy) were used over subjective definitions (clinical diagnosis). If multiple objective definitions of the outcome were presented, estimates that used the most rigorous definition (e.g. highest PMN counts) were included in the analysis.

Quality Assessment: While the Cochrane Collaboration tool for assessing the quality and bias is widely used for randomized control trials [6], no standard tool exists for evaluating the quality of observational studies. However, several criteria have been outlined as important areas to consider for potential bias in observational studies [7]. Based on these criteria, we assessed the source population, selection of participants, strength of the exposure measurement, strength of the outcome measure, control for confounding, if the association of interest was a primary or secondary analysis, and other potential biases (e.g., possible conflicts of interest) of each study. Because of reported concerns about quality assessment scales that assign a numerical score [7], we chose to provide studies with an overall score of poor, fair or good based on the defined criteria areas. Due to the lack of a standardized rating mechanism, we assigned the ratings based on expert knowledge of the topic area and study techniques. Studies were designated as good if no more than two of the above criteria were assigned a fair rating, as fair if three or more of the

criteria were assigned a fair rating, and as poor if two or more of the criteria were assigned a poor rating (Appendix B for full rating scheme).

Data Analysis: Data were aggregated across studies for each syndrome to determine an overall summary estimate using random effects models. This approach assumes that the studies in the analysis are a sample of a larger population of studies and incorporates an estimate of between-study variance as well as within-study variance, producing a more conservative estimate. Studies in which findings had a zero cell were included in the meta-analysis by assigning a 0.5 as the cell count in order to provide an effect estimate and 95% confidence interval (CI). All models were executed first using crude estimates only and subsequently using the adjusted estimate for studies that provided them. All data presented are from the model incorporating the adjusted estimate where available and crude estimates for studies that did not provide an adjusted estimate.

Heterogeneity between studies was assessed using the I^2 statistic, which does not depend greatly on the number of studies in the analyses. I^2 indicates the proportion of the total variation in the estimates that is due to variation between studies rather than to chance; values less than 30 percent were considered minimal heterogeneity and values greater than 50 percent were deemed considerable heterogeneity [8]. If there was substantial heterogeneity, a sensitivity analysis was conducted for each of the subgroups by method of exposure measurement (NAATs and serology) to determine if this significantly changed the association with the outcomes.

Funnel plots were used to provide a visual assessment of the presence of possible publication bias. To aid in the interpretation of the funnel plots, we performed the Begg adjusted rank correlation test, a numerical analogue to the funnel plot [9]. To account for the potentially lower power of the Begg test, we also performed the Egger et al. regression asymmetry test [10].

All data analyses were conducted using STATA 13.1. These analyses of published literature did not require Institutional Review Board approval.

RESULTS

Overall, the systematic search for studies of *M. genitalium* and female reproductive tract disease syndromes returned a total of 822 titles, 266 of which evaluated cervicitis, 177 assessed infertility, 117 were on pregnancy outcomes, and 262 studied PID. Each systematic review and meta-analysis is described separately below.

M. genitalium and Cervicitis

After exclusion of duplicate citations from the databases, 158 potentially eligible references to studies reporting on *M. genitalium* and cervicitis were identified (Fig. 1). Of these, 137 were excluded based on a review of the titles, abstracts, and publication language. Three additional studies were excluded following full-text review; one did not provide data on the association between *M. genitalium* and cervicitis [11], one evaluated an outcome other than cervicitis [12], and one did not provide sufficient data to determine the association between *M. genitalium* and cervicitis [13].

A total of nineteen studies were included in the meta-analysis of the association between cervicitis and *M. genitalium* and a summary of the included studies can be found in Table 1. Of the studies included for the cervicitis analysis, nine were designated as good [14-22] and ten were designated as fair [23-32] in terms of methodologic quality (Appendix C). Adjusted effect estimates were provided in nine studies [14, 16, 18, 19, 21, 22, 27, 31, 32]. Seven studies reported crude effect estimates in the original text [17-20, 22, 25, 32], and 11 studies reported

data that allowed us to calculate crude effect estimates [14, 15, 21, 23, 24, 26-31]. Authors were contacted for more information for two of the studies [16, 19] and one provided additional information to calculate a crude effect estimate [19]. Sixteen studies used polymerase chain reaction (PCR) [14-17, 19-28, 30, 31], two studies employed the transcription-mediated amplification (TMA) assay [29, 32] and one study used both TMA and PCR to detect *M. genitalium* [18]. Eight studies employed a microbiological definition of cervicitis [15-17, 19, 21, 25, 26, 28], six studies employed a clinical definition of cervicitis [18, 20, 22, 27, 29, 32], and five studies used a combination of microbiologic and clinical definitions [14, 23, 24, 30, 31]. Three of the studies used a case-control study design [24, 27, 31] while the remaining sixteen used a cross-sectional study design [14-23, 25, 26, 28-30, 32].

In the meta-analysis of all 19 included studies, there was a statistically significant association between *M. genitalium* and cervicitis with a pooled estimate of 1.69 (95% CI: 1.36, 2.10) (Fig 2). There was only moderate evidence of between-study heterogeneity (I^2=58.8% (95% CI: 31.6%, 75.2%), and no significant publication bias (Begg p-value=0.35, Egger p-value=0.53). In sub-analyses, there was no substantial difference in the pooled effect estimate or the I^2-statistic when stratified by geographic location of the study (USA vs. non-USA), study design (case-control vs. cross-sectional), the assay used (PCR vs. TMA) or the definition of cervicitis (microbiologic vs. clinical) (data not shown).

M. genitalium and Female Infertility

After exclusion of duplicate citations from the databases 102 potentially eligibly references were identified (Fig. 3). Ninety-four references were excluded based on title and abstract review. Three studies were excluded following full text review; one study had no

comparison group [33], one study did not detect any *M. genitalium* in the patients [34], and one study detected *M. genitalium* in only one patient [35].

A total of five studies were included in the meta-analysis of the association of *M. genitalium* and female infertility and are summarized in Table 2. Of the studies included in the female infertility analysis, three were designated as good [36-38] and two were designated as fair [39, 40] in terms of methodologic quality (Appendix C). Adjusted effect estimates were reported in three studies [36-38], two studies reported a crude effect estimate [36, 37] and crude effect estimates were calculated from available data for three studies [38-40]. Four studies evaluated women attending fertility clinics, comparing confirmed tubal factor infertility (TFI) to other causes of infertility through laparoscopy, culdoscopy or hysterosalpingography (HSG) [36, 37, 39, 40]. One study evaluated women with clinically diagnosed PID and infertility was defined as sexually active women who were not pregnant after 12 months of follow-up despite rare or no use of contraceptives [38]. Two of the studies had relatively small sample sizes (n=74 [40] and n=106 [39]), two had moderate sized samples (n=194 [37] and n=241 [36]) and one had a fairly large sample (n=586 [38]). Three of the studies detected *M. genitalium* infection using serology [36, 37, 39] and two of the studies used PCR [38, 40]. Four of the studies used a case-control study design [36, 37, 39, 40] and one employed a cross-sectional design [38].

In the meta-analysis of all five included studies, the pooled OR was 2.43 (95% CI: 0.93, 6.34), although this was not statistically significant (Fig 4). There was high between-study heterogeneity (I^2=80.2% (95% CI: 53.5%, 91.6%)), but no significant publication bias (Begg p-value=0.62, Egger p-value=0.70). The earliest study had notably different findings using a first generation serology assay and was identified as a possible outlier [39]. In a sub-analysis excluding this study, the association between *M. genitalium* and female infertility was stronger

and statistically significant (pooled OR 3.46 (95% CI: 1.51, 7.93)). Exclusion of this potential outlier also reduced the level of heterogeneity to modest (I^2=64.4% (95% CI: 0.0%, 87.6%)).

M. genitalium and Pregnancy Outcomes

After exclusion of duplicate citations from the databases, 85 potentially eligibly references were identified (Fig. 5). Seventy-three references were excluded based on review of title, abstract, or publication language. Three studies were excluded following full text review; one study did not provide data on the association between *M. genitalium* and pregnancy outcomes [41], one study did not have a comparison group [42], and one study did not detect *M. genitalium* in the participants [43].

A total of nine studies met the inclusion criteria for pregnancy outcomes (Table 3), but only eight were included in the quantitative meta-analysis. Seven of these studies were designated as good [44-50] and two were designated as fair [14, 51] in terms of methodologic quality (Appendix C). One study assessed ectopic pregnancy and was evaluated separately [47]. All eight studies included in the meta-analysis presented information on preterm birth or spontaneous abortion. Two of the studies presented additional information on the association of *M. genitalium* and stillbirth [44, 50]. All of the outcomes were defined clinically. Adjusted effect estimates were reported in three studies [48-50], five studies reported a crude effect estimate [44, 48-51] and crude effect estimates were calculated from available data for three studies [14, 45, 46]. Seven of the studies assessed *M. genitalium* using PCR [14, 44-46, 49-51] while only one study used TMA [48]. Three of the studies used a case-control study design [44, 48, 49], three used a cohort design [45, 46, 51], and two used a cross-sectional design [14, 50].

In the primary meta-analysis of the eight included studies, we evaluated a combined outcome of either preterm birth or spontaneous abortion, assuming each constituted some form of premature expulsion of the fetus. There was a statistically significant association between *M. genitalium* and the combined outcome of preterm birth and spontaneous abortion with a pooled OR of 1.90 (95% CI: 1.38, 2.60)). In analyses separated by the type of outcome, the associations with *M. genitalium*, remained statistically significant with a pooled OR for preterm birth of 1.95 (95% CI: 1.30, 2.91), and a pooled OR for spontaneous abortion of 1.82 (95% CI: 1.10, 3.03)) (Fig 6). There was low between-study heterogeneity (I^2=0.0% (95% CI: 0.0%, 34.2%)), and no significant publication bias present (Begg p-value=1.00, Egger p-value=0.93). The case-control study on ectopic pregnancy [47] used serology to detect *M. genitalium* and reported no association (AOR 1.0 (95% CI: 0.5, 2.0)). The two studies that also presented data on the association of *M. genitalium* and stillbirth demonstrated no statistically significant associations with ORs of 1.07 (95% CI: 0.42, 2.42) [44] and 1.36 (95% CI: 0.76, 2.45) [50].

M. genitalium and PID

After exclusion of duplicate citations from the databases 167 potentially eligibly references were identified (Fig. 7). One hundred fifty references were excluded based on a review of title, abstract, and publication language. A further seven studies were excluded following full-text review; two studies did not have a comparison group [33, 52], one study had the same population as another more complete study [53], one study did not have an uninfected comparison group [54], one study did not have a clinically defined outcome (i.e. history of PID) [49], one study did not have a comparison group without PID [55], and one study was a reprint of another included study [56].

A total of ten studies were included in the meta-analysis of the association between *M. genitalium* and PID and are summarized in Table 4. Of the studies included in the PID analysis, five were designated as good [20, 38, 47, 57, 58] and five were designated as fair [31, 59-62] in terms of methodologic quality (Appendix C). Adjusted effect estimates were presented in the text for four studies [31, 38, 47, 58], four presented a crude estimate [20, 38, 47, 62], and crude effect estimates were calculated from available data for six studies [31, 57-61]. Seven studies assessed *M. genitalium* using PCR [31, 38, 57, 58, 60, 62], two studies used serology [47, 59], and one study used PCR and serology [61]. Two studies microbiologically defined their outcome as endometritis [38, 57], two of the studies used laparoscopy (with or without clinical diagnoses) and defined their outcome as salpingitis [59, 61], and the remaining six studies clinically defined their outcome as PID [20, 31, 47, 58, 60, 62]. Five of the studies used a case-control study design [31, 47, 57, 58, 60], four of the studies used a cross-sectional design [20, 38, 59, 61], and one of the studies used a cohort design [62].

In the meta-analysis of all ten included studies, there was a statistically significant association between *M. genitalium* and PID with a pooled OR of 2.14 (95% CI: 1.31, 3.49) (Fig 8). There was only moderate evidence of between-study heterogeneity (I^2=51.3% (95% CI: 0.0%, 76.3%) and no significant publication bias (Begg p-value=0.98, Egger p-value=0.055).

DISCUSSION

This meta-analysis of the published literature on the association of *M. genitalium* and female reproductive tract disease was remarkably consistent, and demonstrated an approximately two-fold increase in risk across all syndromes, with pooled estimates ranging from 1.7 to 2.4. These pooled estimates were all statistically significant, with the exception of analyses of

infertility. In contrast, the number of studies evaluating the association between *M. genitalium* and stillbirth (n=2), as well as those evaluating the association between *M. genitalium* and ectopic pregnancy (n=1) was too small to draw definitive conclusions. In all analyses, the pooled estimates generated from the crude effect estimates were not substantially different than those derived from the adjusted effect estimates (when available), highlighting the robustness of these results.

One previous meta-analysis of the association between *M. genitalium* and cervicitis [1], and one systematic review [2] were published in 2011. Our analysis included an additional eight studies of cervicitis [19-21, 23, 27, 30-32], five of PID [20, 31, 59, 61, 62], two of infertility [38, 39], and three of pregnancy outcomes [14, 46, 50]. The addition of these new studies allowed quantitative synthesis of the literature and extended earlier qualitative assessments suggesting that *M. genitalium* was related to each of these four female reproductive tract disease syndromes by confirming statistically significant associations in most cases.

The pooled estimate for the association between *M. genitalium* and cervicitis that we observed here (summary estimate=1.7) was similar to that observed in the earlier systematic review [2] and the previous meta-analysis, which also employed a random effects model (pooled estimate 2.2 (95% CI: 1.6-2.9)) [1]. This was despite the exclusion of three of the studies in the original meta-analysis that did not meet our inclusion criteria (one study was not in English [63], one study did not report on cervicitis but was included in the PID analysis [58], and one study evaluated the association between cervical HIV-1 DNA shedding and *M. genitalium* infection, not cervicitis [64]) and the inclusion of an additional eight studies published since then [19-21, 23, 27, 30-32]. Similar to other known STIs such as *Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis*, the evidence from systematic reviews and meta-

analysis is consistent with an association of *M. genitalium* with cervicitis, and this was true across the wide range of clinical and microbiological definitions of cervicitis as well as varying detection methods for *M. genitalium*. Overall, the evidence suggests that *M. genitalium* should be considered in differential diagnoses of cervicitis.

In the United States 1 in every 8 infants is born prematurely [65] and this is due to numerous causes [66]; infectious agents typically contribute to only a small proportion of preterm births. Therefore, it was remarkable that we observed a two-fold increase in risk for preterm birth and spontaneous abortion. This finding was consistent with the earlier systematic review [2], and included an additional three studies of pregnancy outcomes [14, 46, 50]. Our decision to consider preterm delivery (<37 weeks gestation) and spontaneous abortion (<16 weeks gestation) together as conditions due to a similar mechanism (premature expulsion of the fetus) was supported by the consistency of the effect estimates in stratified and combined analyses. Nevertheless, while this suggests that *M. genitalium* may cause adverse pregnancy outcome, the prevalence of this organism in low risk populations is generally low (2.0%) [2, 3]. Therefore, in considering whether pregnant women should be screened for *M. genitalium,* limiting this to high risk pregnant women may be preferable.

Risk for PID was twice as high among women with *M. genitalium* in this meta-analysis, consistent with earlier qualitative assessments [2], and this analysis incorporated an additional five studies published since the last review [20, 31, 59, 61, 62]. Notably, two excluded studies that recently reported the greatest risk for PID were conference abstracts that did not meet the inclusion criteria for our meta-analysis [67, 68], suggesting that our summary estimate of 2.1 may be an underestimate. While *N. gonorrhoeae* and *C. trachomatis* are known causes of PID and account for a third to a half of all cases, our findings indicate that we may need to consider

M. genitalium as well as *N. gonorrhoeae* and *C. trachomatis* when recommending treatment for PID. However, current treatment recommendations for PID do not include antibiotics that are effective against *M. genitalium* [69], and antimicrobial therapy that is more active against *M. genitalium* (e.g., azithromycin or moxifloxacin) may be effective in some persistent cases of PID.

In the United States approximately 11% of women age 15-44 have impaired fecundity [70] and *M. genitalium* was associated with an over three-fold increased risk of infertility in this study. This increased risk was similar to the qualitative observations from the prior systematic review [2], and accounted for two additional studies of infertility [38, 39]. Notably, one study included in our meta-analysis compared women with infertility from all causes (tubal obstruction, unexplained infertility, male infertility, and ovulation disorders) to women with proven fertility [40]. The information reported in the paper did not allow us to exclude failure to conceive due to male infertility and this may have reduced the pooled effect estimate for infertility. Given the small number of studies on *M. genitalium* and infertility as well as the instability of the summary estimate in the main and sub-analyses, more studies on this topic are warranted.

While a multitude of studies evaluating the association between *M. genitalium* and nongonococcal urethritis in men exist, and a substantial number assessing the relationship with cervicitis in women, relatively little has been done to define the association between *M. genitalium* and stillbirth or ectopic pregnancy. Considering the prevalence of stillbirth can range from 0.5% in developed countries to more than 3% in less developed countries, this is an important area of future research [71]. Additionally, since only one study has evaluated the

association between *M. genitalium* and ectopic pregnancy, no clear conclusions could be drawn. Further research on both of these topics would be beneficial.

All studies included in these meta-analyses were assessed for quality based on defined criteria (Appendix B and C) and all met criteria for good or fair. Since none of the included studies were considered poor, no sensitivity analyses excluding poor quality studies were done. Quality ratings were tied to the use of the study data for the analysis of a given syndrome and do not necessarily reflect the intrinsic quality of the study itself. Because of this, in some cases the same study received different quality ratings when it was included in more than one analysis if the quality of the information provided differed for individual outcomes.

A major strength of these meta-analyses was our ability to calculate a pooled estimate for each outcome, summarizing studies with varying exposure and outcome measurements and different populations. However, there are several possible limitations to the use of meta-analysis to determine the association between *M. genitalium* and female reproductive tract disease syndromes. Given its relatively recent emergence, less literature has characterized *M. genitalium*'s association with female reproductive health outcomes than other STIs, and the were number of studies was not sufficient to explore stratified analyses for all of the pregnancy outcomes, PID, and female infertility. However, it was possible to evaluate subgroups for cervicitis, and none of the subgroups were substantially different than the full pooled estimate, lending confidence to our results. Despite a variety of exposure measures (NAATs vs. serology), and outcome definitions, heterogeneity as measured by the I^2-statistic was moderate to low in all of the analyses presented. The heterogeneity that was present reflected heterogeneity in point estimates rather than study characteristics; however, analyzing these studies as a whole instead of by subgroup characteristics was a necessity due to small numbers of studies for most outcomes.

A number of studies presented unadjusted results and several of the estimates had to be calculated from available data. Our observations that the associations were robust across crude and adjusted effect estimates lends further confidence to these results. A possible limitation to all meta-analyses is the influence of publication bias on the overall pooled estimates. Although publication bias based on statistical tests was not significant for any of the outcomes evaluated, since *M. genitalium* is an emerging STI, authors may be hesitant to publish articles showing a lack of a significant association, and our pooled estimates may overestimate the true effect to some degree.

Our meta-analyses suggest a significant association between *M. genitalium* and cervicitis, pregnancy outcomes (preterm birth and spontaneous abortion) and PID. Additionally, our analysis strongly suggests a possible association between *M. genitalium* and female infertility. These associations with adverse reproductive health outcomes suggest that screening high-risk women for *M. genitalium* may be warranted.

FIGURES

Figure 1: Flow diagram of studies of the association between *M. genitalium* and cervicitis

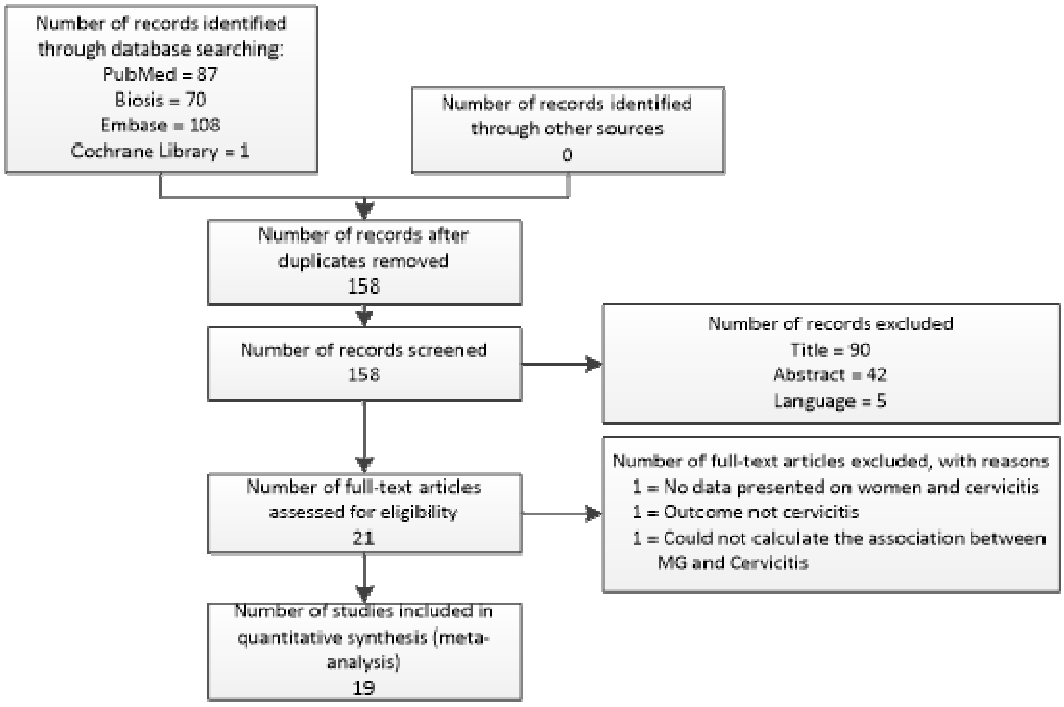


Table 1: Studies with data on the association between *M. genitalium* and cervicitis (n=19)

Author, year	Study Location	Study Design	Study Population	Sample Size	Assay	Definition of Cervicitis	Crude Effect Estimate†	Adjusted Effect Estimate	Variables Adjusted For
Palmer H M, 1991[23]	United Kingdom	Cross-sectional	Women age 16-40 attending the Genitourinary Medicine Clinic	54	PCR	Observable inflammation and cervical mucopurulent discharge and/or ≥20 PMNL/HPF	*OR 0.33 (95%CI: 0.06, 1.78)	ND	ND
Uno M, 1997 [24]	Japan	Case-Control	Women age 19-49 visiting the OB/GYN department and Ladies Clinic. Cases: Symptomatic women Controls: Healthy pregnant women 27-33 weeks gestation	67 cases, 80 controls	PCR	Purulent or mucopurulent endocervical discharge or ≥20 PMNs/HPF	*OR ∞ (95% CI: 2.0, ∞)	ND	ND
Casin I, 2002 [25]	France	Cross-sectional	Consecutive women presenting with genital symptoms at an STD clinic	170	PCR	≥10 PMNs/HPF	OR 1.54 (95% CI: 0.81, 2.91)	ND	ND
Manhart 2003 [14]	Washington, U.S.A	Cross-sectional	Women aged 16-45 attending STD Clinic	719	PCR	Presence of either visible yellow mucopus or ≥30 PMNL/1000X HPF	*OR 2.31 (95% CI: 1.23, 4.29)	AOR 3.3 (95% CI: 1.66, 6.40)	Age, proliferative phase of the menstrual cycle, other known causes of cervicitis
Pepin J, 2005 [22]	Ghana/Benin	Cross-sectional	Female sex workers recruited at FSW/STI clinics	597	PCR	Pus on the cervical swab	OR 2.6 (95% CI: 1.5, 4.5)	AOR 1.6 (95% CI: 1.0, 2.7)	Other pathogens, bleeding after sampling, inflammatory cervix, cervical motion tenderness, age
Falk L, 2005 [26]	Sweden	Cross-sectional	All female STD Clinic attendees	455	PCR	More PMNL than epithelial cells in wet smear	*OR 2.37 (95% CI: 0.97, 5.69)	ND	ND
Anagrius C, 2005 [15]	Sweden	Cross-sectional	Consecutive STD clinic attendees	311	PCR	≥30 PMNLs/HPF observed in >4 fields	*OR 4.41 (95% CI: 1.35, 15.53)	ND	ND
Korte J E, 2006 [27]	Texas, U.S.A	Case-control	Minority women with an active curable STI at public health clinics Cases‡: PCR positive for MG Controls: PCR & culture negative for MG	257 cases, 107 controls	PCR	Cervical discharge characterized as yellow or green, or mucoid or creamy	*OR 0.98 (95% CI: 0.22, 5.98)	AOR 0.65 (95% CI: 0.15, 2.9)	Co-infection, age, pregnancy status, intervention group
Pepin J, 2006 [16]	West Africa	Cross-sectional	Women attending health centers in Ghana, Guinea, Mali, and Togo for vaginal discharge	1570	PCR	≥30 PMNL/HPF	Crude not calculated and could not be calculated from article	AOR 2.0 (95% CI: 1.1, 3.7)	Age, presence of other pathogens
Hogdahl M, 2007 [28]	Sweden	Cross-sectional	Women attending a university hospital clinic and the STI clinic	403	PCR	≥30 PMNL/HPF	*OR 1.45 (95% CI: 0.55, 3.56)	ND	ND
Huppert J S, 2008 [29]	Ohio, U.S.A	Cross-sectional	Adolescent women 14-21 years of age at an urban, hospital-based Teen Health Center or Emergency Department	331	TMA	Presence of mucopurulent cervicitis and/or friability	*OR 0.80 (95% CI: 0.41, 1.50)	ND	ND
Moi H, 2009 [17]	Norway	Cross-sectional	Women who voluntarily attended a drop-in STI clinic	6650	PCR	>30 PMNLs/HPF	OR 1.3 (95% CI: 1.0, 1.6)	ND	ND
Gaydos C, 2009 [18]	Maryland, U.S.A.	Cross-sectional	Women attending 2 city STD clinics	322	PCR and TMA	Cervical discharge, including mucopurulent discharge, or cervical friability or otherwise indicated a diagnosis of cervicitis on medical record	OR 2.75 (95% CI: 1.56, 4.86)	AOR 2.41 (95% CI: 1.32, 4.40)	CT, NG, TV, contact referral BV
Falk L, 2010 [30]	Sweden	Cross-sectional	Women attending an STD clinic	131	PCR	More PL than epithelium cells, friability/pus or *portio cervicis*, or ≥30 PL/HPF	*OR 1.58 (95% CI: 0.38, 7.74)	ND	ND
Lusk M J, 2011 [19]	Australia	Cross-sectional	Women attending one of two STI clinics	527	PCR	>30 PMNL/HPF	PR 1.85 (95% CI: 1.52, 2.26)	APR 1.24 (95% CI:	CT

Author, year	Study Location	Study Design	Study Population	Sample Size	Assay	Definition of Cervicitis	Crude Effect Estimate†	Adjusted Effect Estimate	Variables Adjusted For
								1.04-1.48)	
Vandepitte J, 2012 [20]	Uganda	Cross-sectional	Women who engaged in sex work and/or were employed in entertainment facilities from the red-light areas	972	PCR	Presence of mucopurulent endocervical discharge on clinical examination	OR 1.26 (95% CI: 0.84, 1.91)	ND	ND
Bjartling C, 2012 [31]	Sweden	Case-control	Women attending the emergency gynecological outpatient services Cases‡: MG and/or CT positive women Controls: MG and CT negative women, matched on age and month of visit	94 cases, 429 controls	PCR	Pathological saline-prepared vaginal wet smears (more leukocytes than epithelial cells in the absence of clue cells and/or inflammatory vaginitis), or pathological cervical discharge, or friability together with cervical motion tenderness	*OR 3.82 (95% CI: 1.96, 7.32)	AOR 3.8 (95% CI: 2.06, 7.03)	Age, CT
Mobley V L, 2012 [32]	North Carolina, U.S.A	Cross-sectional	English-speaking women age ≥18 recruited from a public STI clinic	239	TMA	Presence of purulent, mucopurulent, or yellow endocervical discharge or endocervical friability on speculum examination	OR 2.10 (95% CI: 1.08-4.10)	AOR 2.11 (95% CI:1.04-4.26)	Age, vaginal discharge, douching, asymptomatic at presentation
Oliphant J, 2013 [21]	New Zealand	Cross-sectional	Women attending four publically funded sexual health clinics for a sexual health screen	229	PCR	≥30 PMNLs on gram stain	*OR 2.33 (0.85, 7.04)	AOR 2.64 (95% CI:0.95-7.34)	Age, ethnicity, clinic attending, symptoms, new sexual partner in last 3 months, cervical mucopus, cervical bleeding

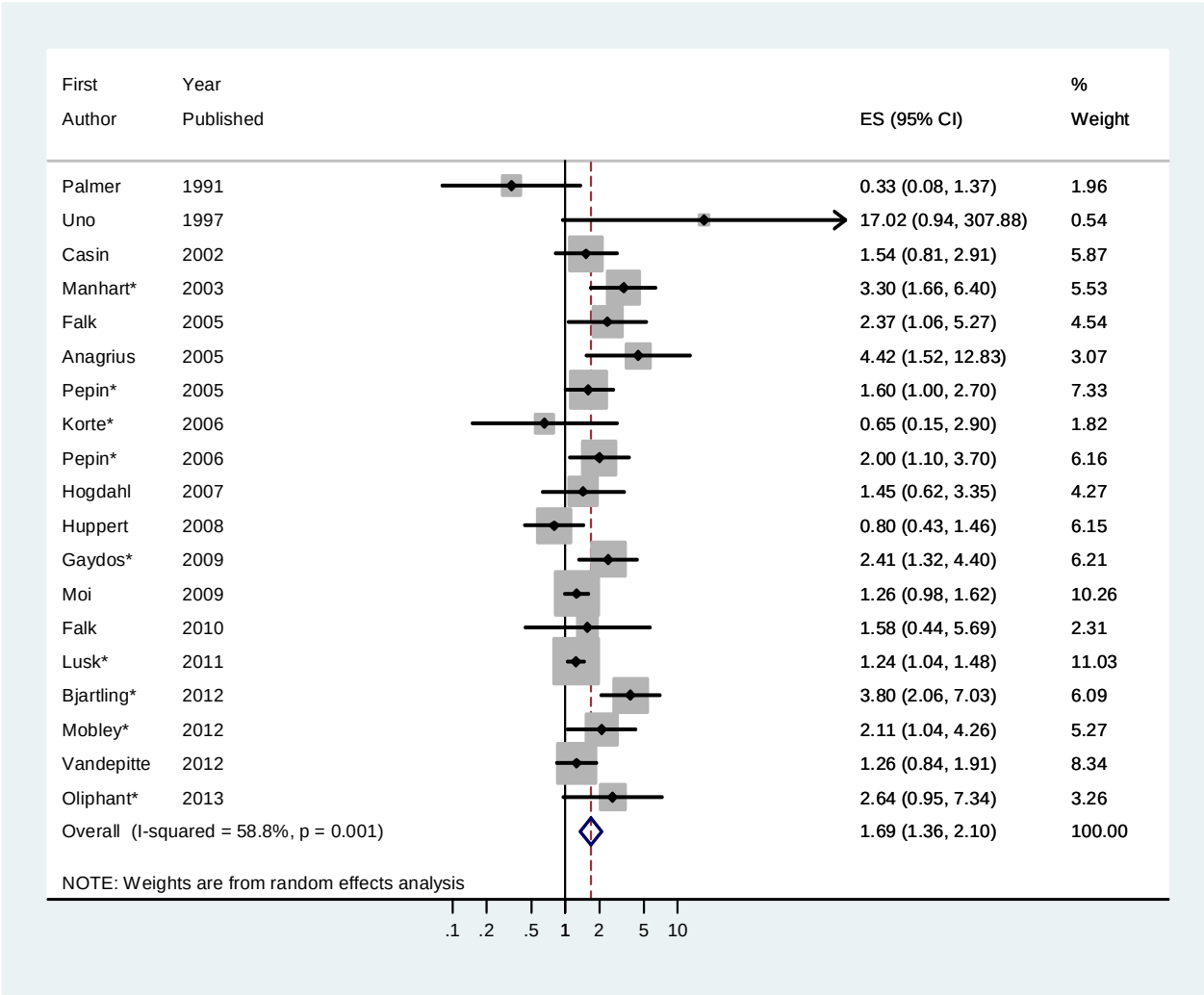
*Calculated from data in article or from data provided by author

† If crude estimate presented in the paper did not match that calculated in STATA using the cell counts, the calculated crude estimate was presented

‡Cases and Controls as defined by author

Abbreviations: ND = Not Done, OR = Odds Ratio, PR =Prevalence Ratio, AOR = Adjusted Odds Ratio, APR =Adjusted Prevalence Ratio, CI = confidence interval, MG = *Mycoplasma genitalium*, CT = *Chlamydia trachomatis*, NG = *Neisseria gonorrhoeae*, TV = *Trichomonas vaginalis*, BV = Bacterial vaginosis, TMA = transcription-mediated amplification assay, PCR = polymerase chain reaction, STI = Sexually transmitted infection, PMNs or PMNL = polymorphonuclear leucocytes, HPF = high-power microscopic field, OB/GYN = obstetrics and gynecology

Figure 2: Association between *M. genitalium* and cervicitis: Forest and Funnel Plots



*Adjusted effect estimate, crude effect estimate in all other cases

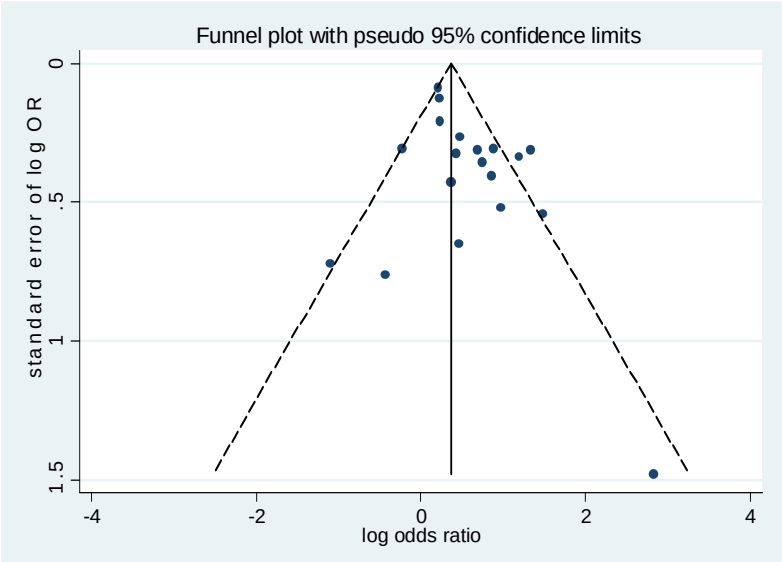


Figure 3: Flow diagram of studies of the association between *M. genitalium* and female infertility

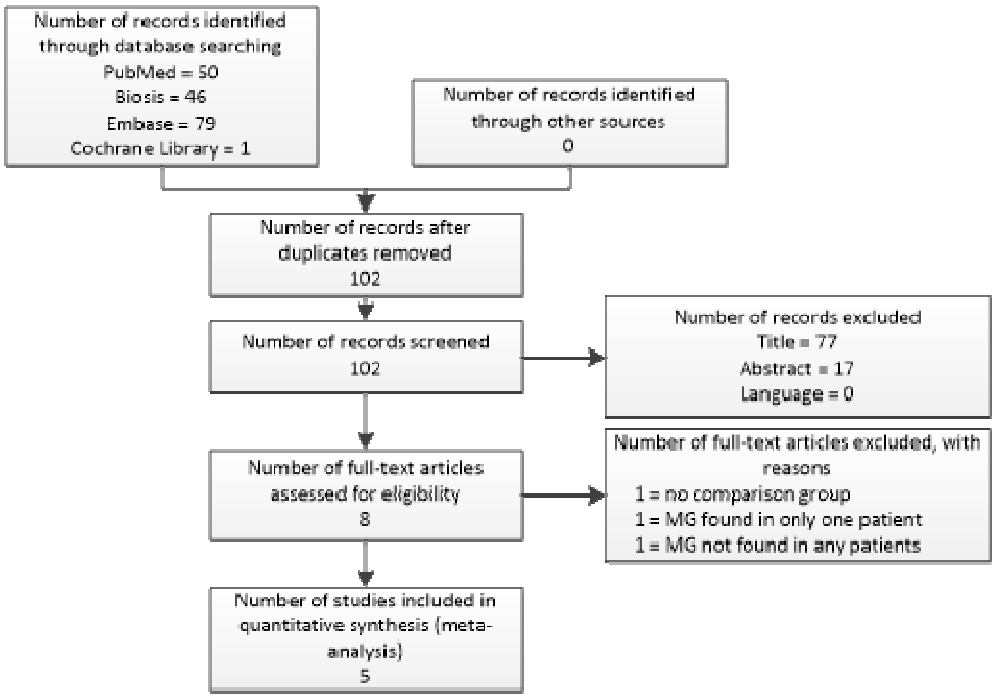


Table 2: Studies with data on the association between *M. genitalium* and female infertility (n=5)

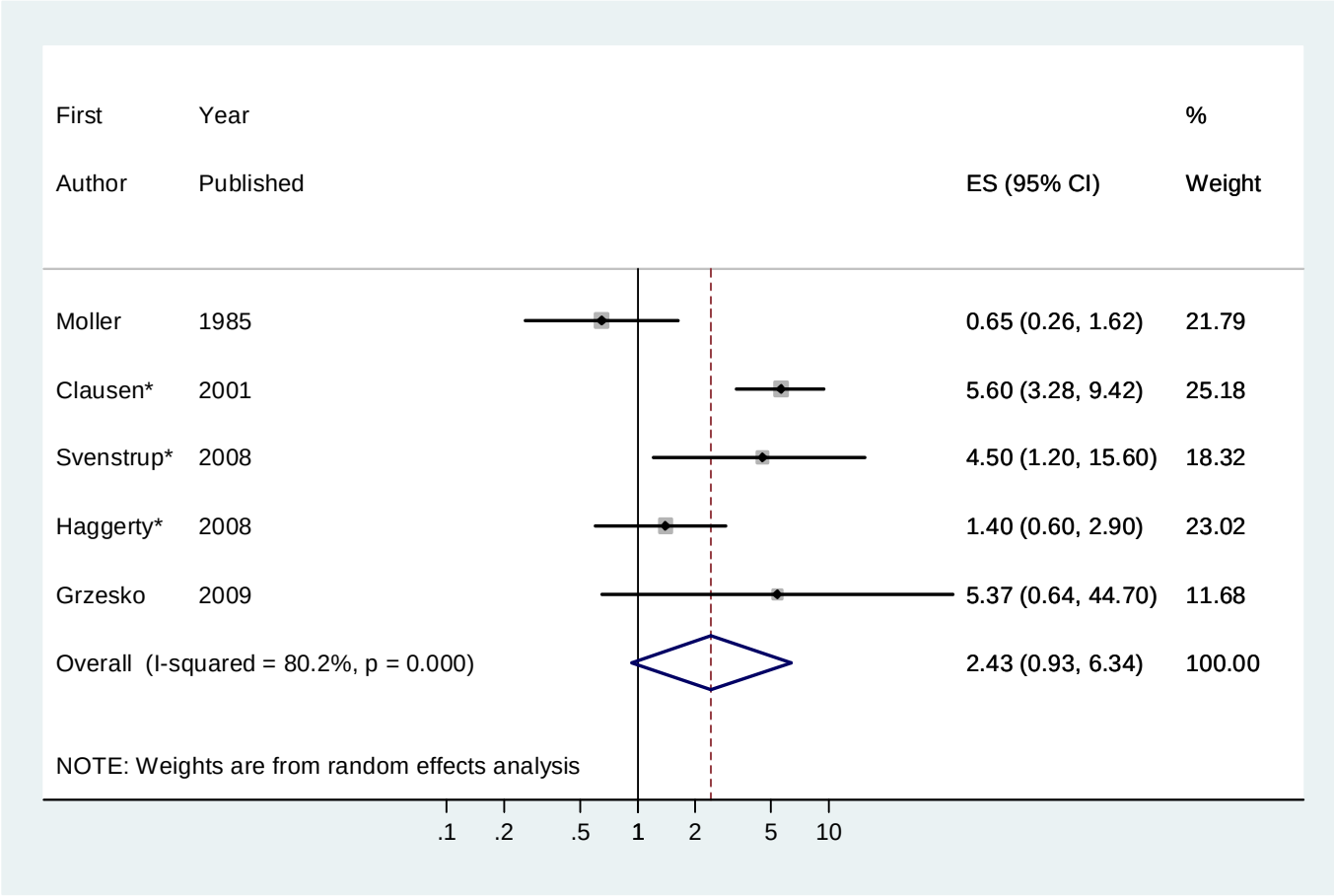
Author, year	Study Location	Study Design	Study Population	Sample Size	Assay	Definition of Infertility	Crude Effect Estimate†	Adjusted Effect Estimate	Variables Adjusted For
Moller, B R 1985 [39]	Denmark	Case-control	Women with a history of infertility for 2 or more years at an out-patient clinic Cases: Abnormal HSG Controls: Normal HSG	45 cases, 61 controls	Serology	Abnormal HSG: includes sactosalpinges, medial occlusions, and peritoneal adhesions	*OR 0.65 (95% CI: 0.23–1.76)	ND	ND
Clausen, H F 2001 [36]	Denmark	Case-control	Women undergoing IVF treatment Cases: confirmed TFI Controls: Women with unexplained infertility	132 cases, 109 controls	Serology	TFI assessed through HSG and laparoscopy to determine if: tubal factor infertility, unexplained infertility, male infertility (severely reduced semen quality)	OR 2.51 (95% CI: 1.14, 5.86)	AOR 5.6 (95% CI: 3.28-9.42)	CT antibodies
Svenstrup, H F 2008 [37]	Denmark	Case-control	Infertile women attending a fertility clinic Cases: confirmed TFI Controls: normal tubes	30 cases, 164 controls	Serology / PCR	TFI assessed through culdoscopy and/or laparoscopy	OR 4.5 (95% CI: 1.3-15.2)	AOR 4.5 (95% CI: 1.2-15.6)	Age, CT antibodies
Haggerty C L, 2008 [38]	USA	Cross-sectional	Women age 14-37 with clinically diagnosed PID	586	PCR	Self-report: sexually active women with at least 12 months of follow up despite rare or no use of contraceptives	*OR 0.87 (95% CI: 0.44, 1.62)	AOR 1.4 (95% CI: 0.6, 2.9)	Age, race, NG, CT, self-reported infertility at baseline
Grzesko, J 2009 [40]	Poland	Case-control	Patients hospitalized for a planned laparoscopy Cases: women with tubal obstruction, unexplained infertility, male infertility (sperm assessment), ovulation disorders Controls: proven fertility	51 cases, 23 controls	PCR	Infertility assessed through laparoscopy	*OR 5.37 (95% CI: 0.67-243.23) *Unexplained infertility vs. controls: OR 9.06 (95% CI: 0.97-426.33)	ND	ND

*Calculated from data in article or from data provided by author

† If crude estimate presented in the paper did not match that calculated in STATA using the cell counts, the calculated crude estimate was presented

Abbreviations: ND = Not Done, OR = Odds Ratio, PR =Prevalence Ratio, AOR = Adjusted Odds Ratio, APR =Adjusted Prevalence Ratio, CI = confidence interval, MG = *Mycoplasma genitalium*, CT = *Chlamydia trachomatis*, NG = *Neisseria gonorrhoeae*, TV = *Trichomonas vaginalis*, BV = Bacterial vaginosis, TMA = transcription-mediated amplification assay, PCR = polymerase chain reaction, STI = Sexually transmitted infection, PMNs or PMNL = polymorphonuclear leucocytes, HPF = high-power microscopic field, TFI = Tubal Factor Infertility, IVF = In vitro fertilization, HSG = hysterosalpingography

Figure 4: Association between *M. genitalium* and female infertility: Forest and Funnel Plots



*Adjusted effect estimate, crude effect estimate in all other cases

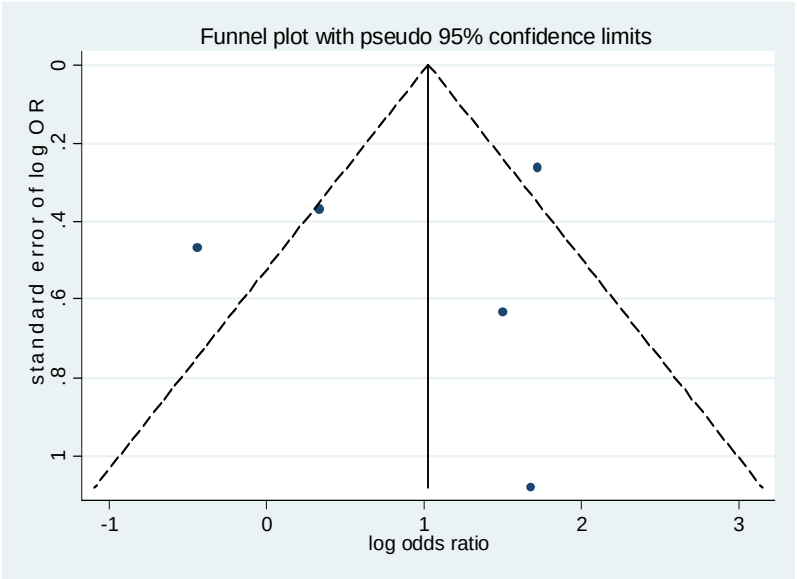


Figure 5: Flow diagram of studies of the association between *M. genitalium* and pregnancy outcomes

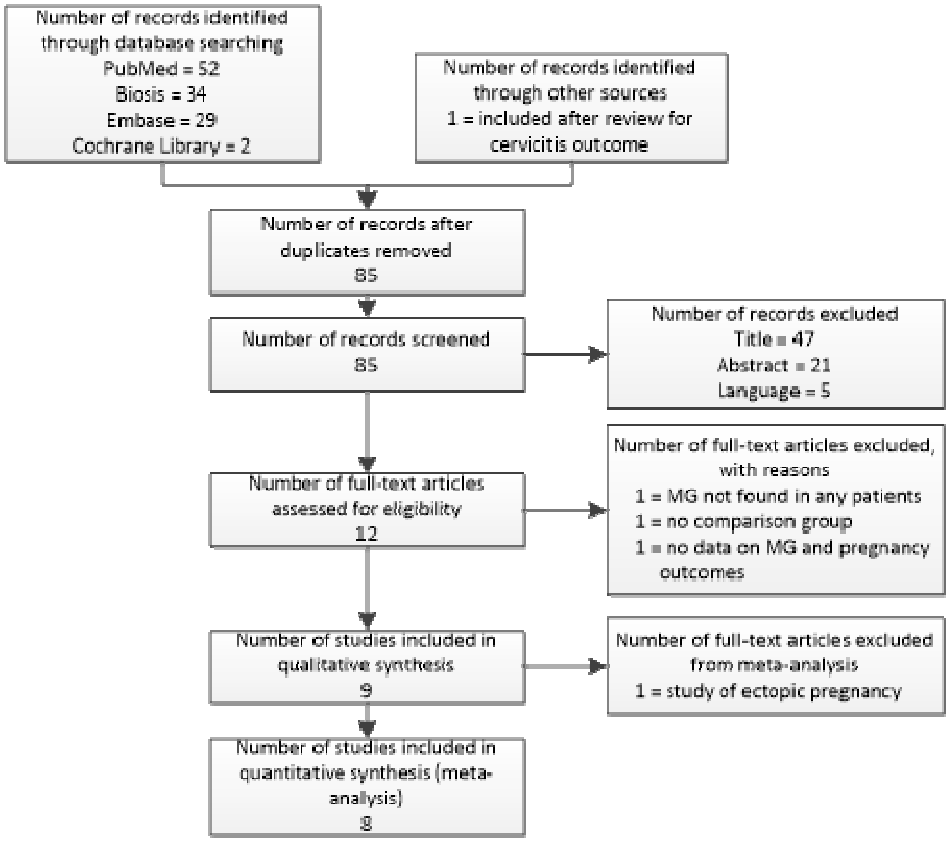
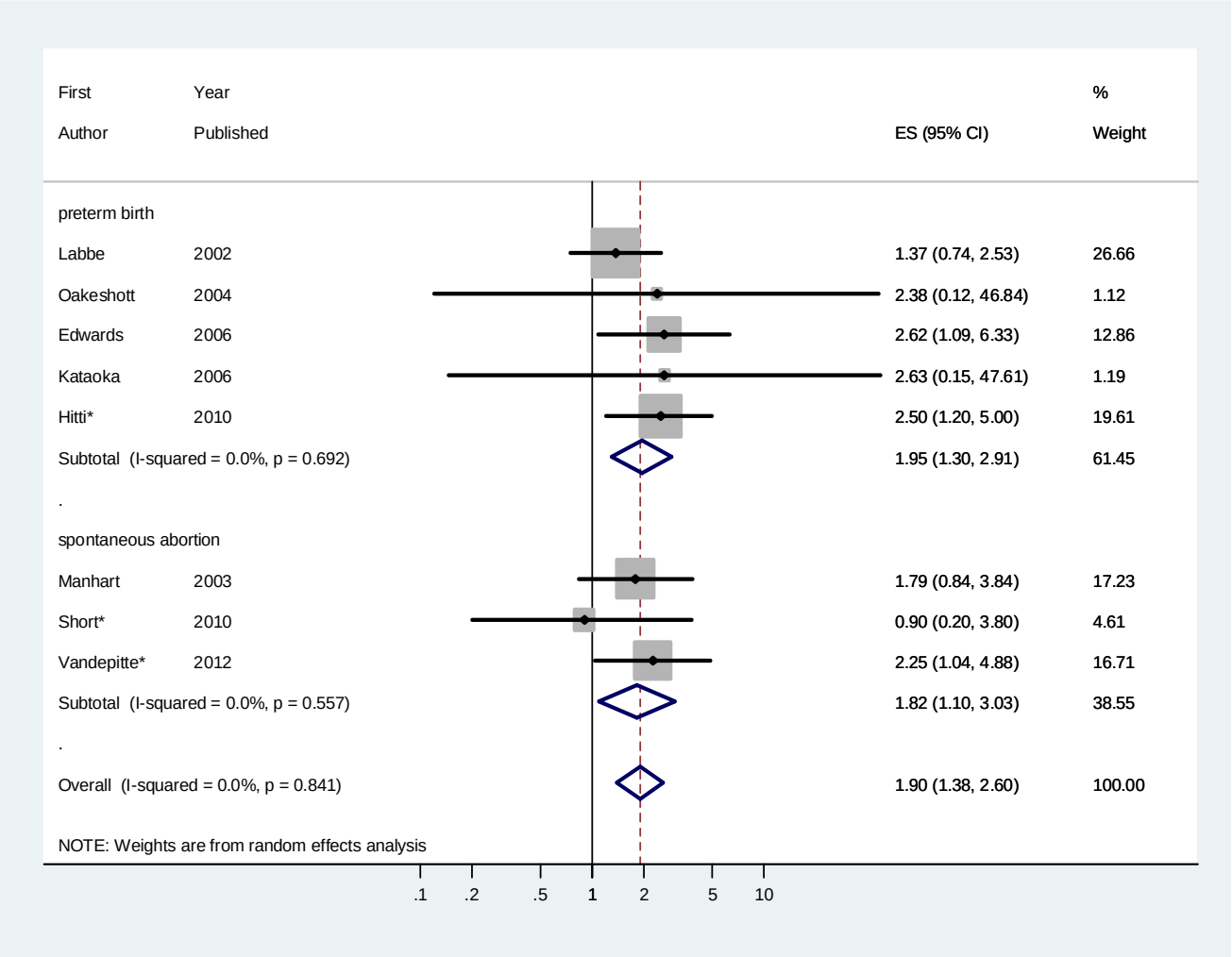


Table 3: Studies with data on the association between *M. genitalium* and Pregnancy and Delivery Outcomes (n=9)

Author, year	Study Location	Study Design	Study Population	Sample Size	Assay	Definition of the pregnancy outcome	Crude Effect Estimate†	Adjusted Effect Estimate	Variables Adjusted For
Labbe A-C 2002 [44]	Guinea-Bissau	Case-control	Cases: Women who gave birth or aborted in obstetrical ward with adverse pregnancy outcomes. Controls: term neonate with weight ≥2500g	Preterm Delivery: 199 cases Stillbirth:125 cases Spontaneous Abortion: 53 cases 600 controls	PCR	Cases classified by: stillbirths, spontaneous abortions, premature deliveries‡	Preterm Delivery = OR 1.37 (95% CI: 0.69-2.60) Stillbirth = OR 1.07 (95% CI: 0.42-2.42) Spontaneous Abortions = OR 0.61 (95% CI: 0.07-2.51)	ND	ND
Manhart L, 2003 [14]	Washington, U.S.A	Cross-sectional	Randomly selected women aged 16-45 attending Sexually Transmitted Disease Clinic for a new problem	719	PCR	Spontaneous Miscarriage: loss of fetus before 20 weeks of gestation	*OR 1.79 (95% CI: 0.73, 3.93)	ND	ND
Oakeshott, P 2004 [45]	England	Prospective Cohort	Consecutive pregnant women of <10 weeks of gestation who presented at 32 general practices and 5 family planning clinics	Miscarriage: 894 Preterm birth: 699	PCR	Miscarriage at <16 weeks Preterm birth at <37 weeks	*Miscarriage RR 1.6 (95% CI: 0.3, 9.8) *Preterm Birth RR 0.00 (95% CI: -, -)	ND	ND
Edwards, R K 2006 [51]	Florida, USA	Prospective Cohort	Women with singleton pregnancies between 23 and 32 weeks of gestation for evaluation of uterine contractions,	134	PCR	Preterm Delivery (<37 weeks)	OR 2.62 (95% CI: 1.09, 6.34)	ND	ND
Kataoka S, 2006 [46]	Japan	Prospective Cohort	Women with singleton pregnancies at <11 weeks, after confirmed normal fetal heartbeat	877	PCR	Preterm Birth: spontaneous abortion or preterm birth at <34 weeks	*RR 0.00 (95% CI: -, -)	ND	ND
Jurstrand M, 2007 [47]	Sweden	Case-Control	Cases: Inpatient women with clinical diagnosis of ectopic pregnancy Controls: Healthy pregnant women being screened for rubella	82 cases, 246 controls	serology (LAMP-EIA)	Ectopic Pregnancy assessed through clinical criteria and confirmed through laparoscopy if uncertain	OR 1.3 (95% CI: 0.7-2.5)	AOR 1.0 (95% CI: 0.5-2.0)	Age, CT
Hitti J, 2010 [48]	Peru	Case-control	Women ≥12 years of age who had presented with spontaneous labor attending a maternity hospital Cases: spontaneous preterm delivery at 20-36 weeks gestation Controls: next consecutive spontaneous term delivery	661 cases, 667 controls	TMA	Preterm Birth: 20-36 weeks gestation	OR 2.5 (95% CI: 1.3-5.0)	AOR 2.5 (95% CI: 1.2-5.0)	Maternal age, cigarette smoking, second trimester bleeding, twin gestation, prior preterm birth
Short V L, 2010 [49]	Pennsylvania, USA	Nested case-control study	Adolescent girls and women 14-40 <22 weeks gestation, attending ED Cases: spontaneous abortion Controls: maintained pregnancy ≥22 weeks	82 cases, 134 controls	PCR	Spontaneous abortion: loss of a conceptus prior to 20 weeks	OR 0.5 (95% CI: 0.1-2.0)	AOR 0.9 (95% CI: 0.2-3.8)	Age, history of spontaneous abortion, smoking, gestational age
Vandepitte J, 2012 [50]	Uganda	Cross-sectional	Women engaged in commercial sex work and/or employed in entertainment facilities	957 among ever pregnant	PCR	Women who had been pregnant but not had a live birth Lifetime Number of Stillbirth (≥1 vs. none)	No live birth: OR 2.96 (95% CI: 1.46-5.99) Stillbirth: OR 1.36 (95% CI: 0.76, 2.45)	AOR 2.25 (95% CI: 1.04-4.88)	Age, use of hormonal contraceptives, NG, *Candida* infection, HIV

*Calculated from data in article or from data provided by author
† If crude estimate presented in the paper did not match that calculated in STATA using the cell counts, the calculated crude estimate was presented
‡ Definitions of outcomes not provided
Abbreviations: ND = Not Done, OR = Odds Ratio, PR =Prevalence Ratio, AOR = Adjusted Odds Ratio, APR =Adjusted Prevalence Ratio, CI = confidence interval, MG = *Mycoplasma genitalium*, CT = *Chlamydia trachomatis*, NG = *Neisseria gonorrhoeae*, TV = *Trichomonas vaginalis*, BV = Bacterial vaginosis, TMA = transcription-mediated amplification assay, PCR = polymerase chain reaction, STI = Sexually transmitted infection, PMNs or PMNL = polymorphonuclear leucocytes, HPF = high-power microscopic field, TFI = Tubal Factor Infertility

Figure 6: Association between *M. genitalium* and pregnancy outcomes, stratified by type of pregnancy outcome (preterm birth vs. spontaneous abortion): Forest and Funnel Plots



*Adjusted effect estimate crude effect estimate in all other cases

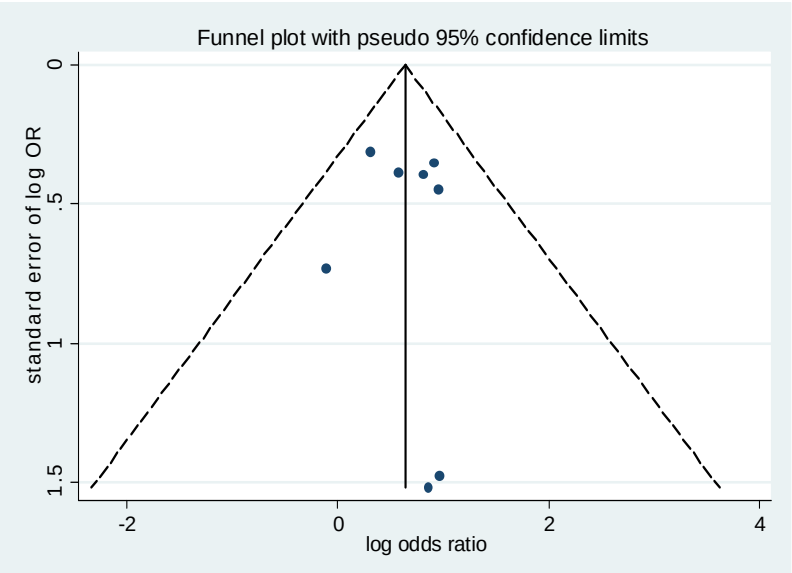


Figure 7: Flow diagram of studies of the association between *M. genitalium* and PID

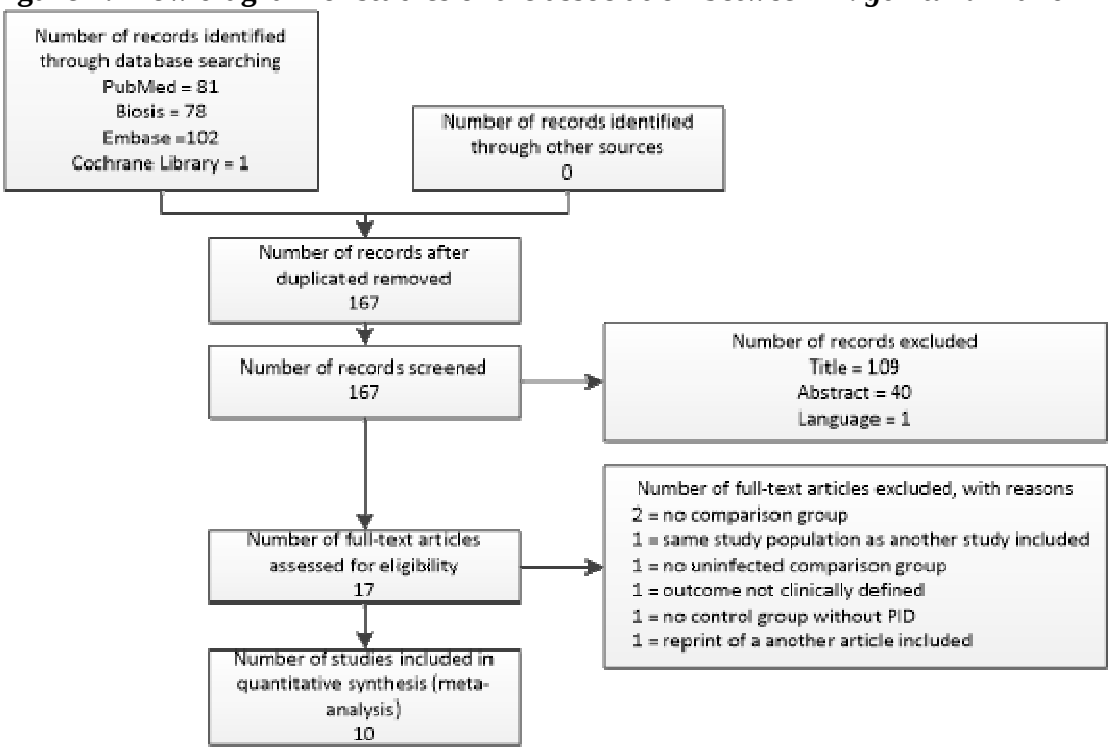


Table 4: Studies with data on the association between *M. genitalium* and PID (n=10)

Author, year	Study Location	Study Design	Study Population	Sample Size	Assay	Definition of PID	Crude Effect Estimate†	Adjusted Effect Estimate	Variables Adjusted For
Lind K, 1987 [59]	Denmark	Cross-sectional	Women with a provisional clinical diagnosis of PID	61	Serology (titre ≥80)	Salpingitis: laparoscopically or clinically defined,	*OR 0.23 (95% CI: 0.01, 4.70)	ND	ND
Cohen C R, 2002 [57]	Kenya	Case-control	Women age 18-40 who presented with low abdominal pain that ≤14 days at STD referral clinic Cases: histologically confirmed endometritis Controls: no endometritis	58 cases, 57 controls	PCR	Endometritis: presence of at least one plasma cell per 120X microscopic field of endometrial or cervical stroma	*OR 10.29 (95% CI: 1.32, 458.62)	ND	ND
Simms L, 2003 [60]	England	Case-Control	Cases: Women age 16-46, patients from a larger study of risk factors associated with PID. Controls: Women attending OB/GYN for bilateral tubal ligation and underwent laparascopy	45 cases, 37 controls	PCR	Clinical PID: lower abdominal pain, adnexal tenderness, and tenderness with motion of the cervix and uterus	*OR ∞ (95% CI: 1.41, ∞)	ND	ND
Jurstrand M, 2007 [47]	Sweden	Case-Control	Cases: Women with a clinical diagnosis of PID who were inpatients Controls: healthy pregnant women screened for rubella	193 cases, 246 controls	Serology (LAMP-EIA)	Clinical PID: pain in the lower abdomen for <3 weeks with a palpable adnexal mass and/or motion tenderness, fever (38.0 C) and objective signs of lower genital tract infection	OR 1.2 (95% CI: 0.69-2.08)	AOR 1.0 (95% CI: 0.6-1.7)	Age, CT
Haggerty C L, 2008 [38]	USA	Cross-sectional (CS) Prospective Cohort	Women age 14-37 with clinically diagnosed PID	CS: 502 Cohort: 586	PCR	Endometritis: ≥5 surface epithelium neutrophils per x400 field absent of menstrual endometrium and/or ≥2 stromal plasma cells per x120 field	CS: OR 2.6 (95% CI: 1.5, 4.6)	CS: AOR 2.0 (95% CI: 1.0, 4.2) Cohort: ARR 6.0 (95% CI: 1.4, 27.1)	CS: Age, race, NG, CT Cohort: Age, NG, CT, race, self-reported partner treatment, sex between visits
Bjartling C, 2010 [58]	Sweden	Case-control	Women seeking termination of pregnancy at outpatient service. Cases: MG positive women Controls: MG and CT negative, matched on age, month of testing, procedure used (medical or surgical)	49 cases, 168 controls	PCR	PID: lower abdominal pain, cervical, uterine or adnexal tenderness at pelvic bimanual examination together with one of the following: pathological vaginal wet smear or yellow pus from the endocervical canal, elevated C-reactive protein >8 or fever >38 C	*OR 5.72 (95% CI: 1.28, 28.53)	AOR 6.29 (95% CI: 1.56, 25.2)	Age, CT
Oakeshott P, 2010 [62]	London, UK	Cohort	Female student ≤27 years of age recruited from 20 universities and further education colleges, who were sexually active, not pregnant, and not tested for C. trachomatis in past 3 months	2246	PCR	Clinical PID: pelvic pain, cervical motion tenderness, and uterine or adnexal tenderness	RR 2.35 (95% CI: 0.74, 7.46)	ND	ND
Bjartling C, 2012 [31]	Sweden	Case-control	Women attending the emergency gynecological outpatient services Case: MG and CT positive women Control: CT and MG negative women, matched on age and month of visit	81 cases, 317 controls	PCR	PID: lower abdominal pain together with cervical and/or uterine and/or adnexal tenderness at pelvic bimanual examination and one of the following: pathological saline prepared vaginal wet smear or pus from the endocervical canal or elevated C-reactive protein or fever	*OR 8.18 (95% CI: 1.14, 91.31)	AOR 9.00 (95% CI: 1.62, 49.89)	Age, CT
Taylor-Robinson D, 2012 [61]	London, UK	Cross-sectional	Women with lower abdominal pain, selected sequentially	109	PCR and serology	Salpingitis confirmed through laparoscopy	*PCR OR 2.13 (95% CI: 0.31, 10.99) *Antibodies OR 2.24	ND	ND

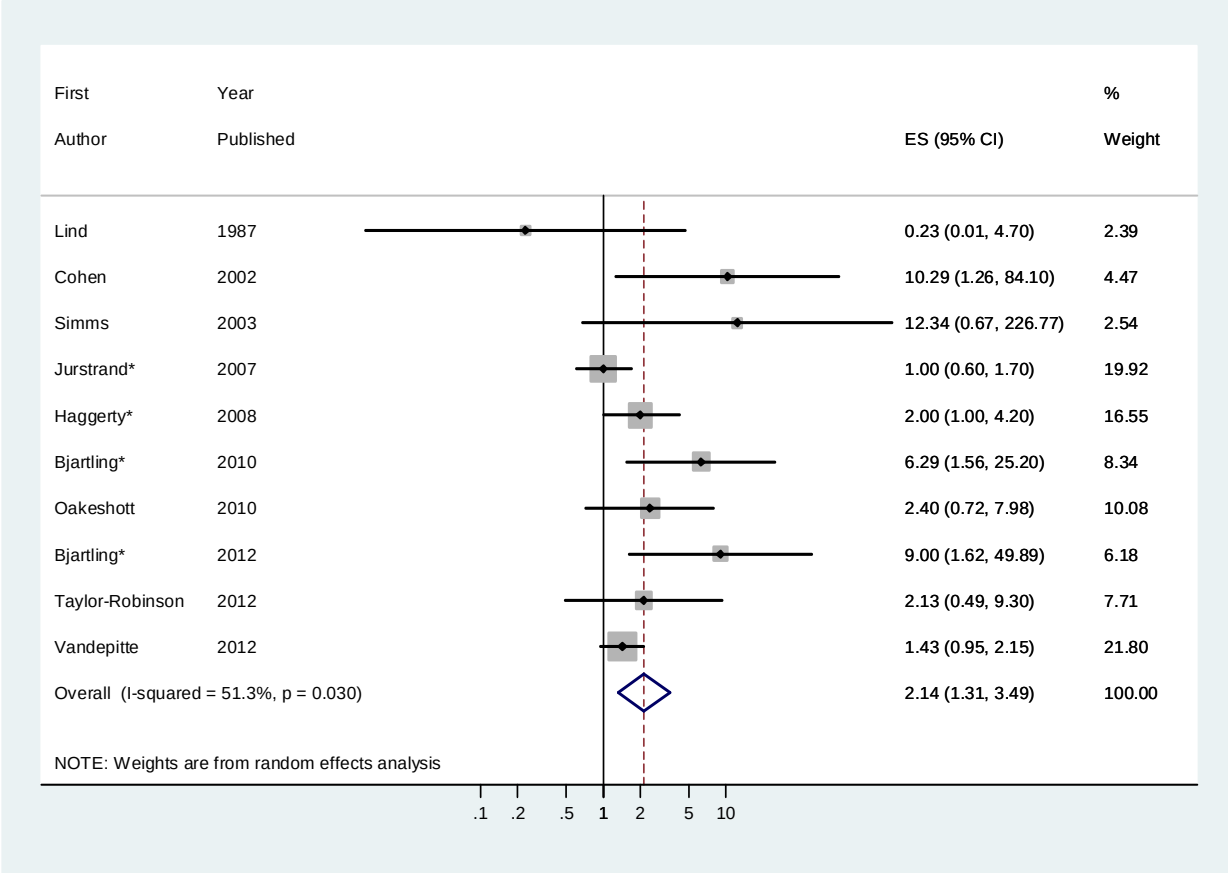
Author, year	Study Location	Study Design	Study Population	Sample Size	Assay	Definition of PID	Crude Effect Estimate†	Adjusted Effect Estimate	Variables Adjusted For
							(95% CI: 0.75, 6.54)		
Vandepitte J, 2012 [20]	Uganda	Cross-sectional	Women who engaged in sex work and/or were employed in entertainment facilities from the red-light areas	972	PCR	PID: reported lower abdominal pain and/or dyspareunia confirmed by bimanual palpation	OR 1.43 (95% CI: 0.95, 2.15)	ND	ND

*Calculated from data in article or from data provided by author

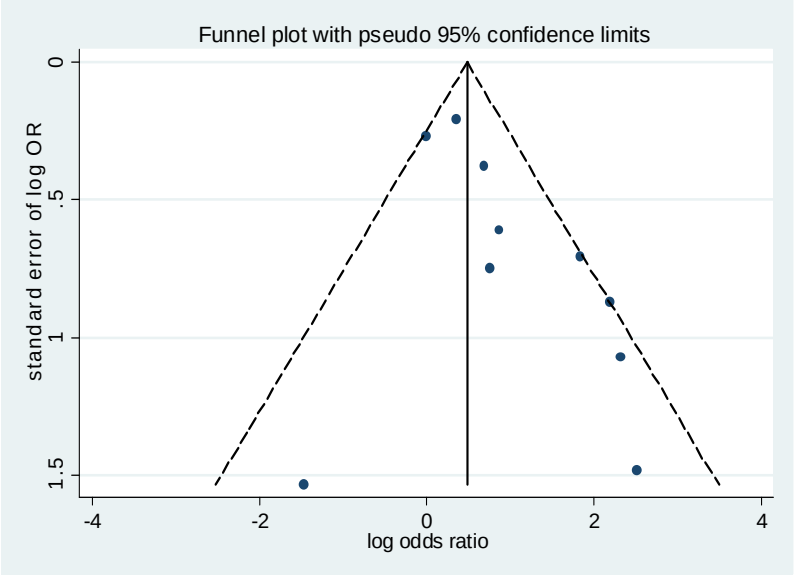
† If crude estimate presented in the paper did not match that calculated in STATA using the cell counts, the calculated crude estimate was presented

Abbreviations: ND = Not Done, OR = Odds Ratio, PR =Prevalence Ratio, AOR = Adjusted Odds Ratio, APR =Adjusted Prevalence Ratio, CI = confidence interval, MG = *Mycoplasma genitalium*, CT = *Chlamydia trachomatis*, NG = *Neisseria gonorrhoeae*, TV = *Trichomonas vaginalis*, BV = Bacterial vaginosis, TMA = transcription-mediated amplification assay, PCR = polymerase chain reaction, STI = Sexually transmitted infection, PMNs or PMNL = polymorphonuclear leucocytes, HPF = high-power microscopic field, TFI = Tubal Factor Infertility, OB/GYN = obstetrics and gynecology

Figure 8: Association between *M. genitalium* and PID: Forest and Funnel Plots



*Adjusted effect estimate, crude effect estimate in all other cases



APPENDICES

Appendix A: Full PubMed Search Criteria

1. ***M. gentialium* and Cervicitis:** ("mycoplasma genitalium"[MeSH Terms] OR ("mycoplasma"[All Fields] AND "genitalium"[All Fields]) OR "mycoplasma genitalium"[All Fields]) AND ("uterine cervicitis"[MeSH Terms] OR ("uterine"[All Fields] AND "cervicitis"[All Fields]) OR "uterine cervicitis"[All Fields] OR "cervicitis"[All Fields])
2. ***M. gentialium* and Infertility:** ("mycoplasma genitalium"[MeSH Terms] OR ("mycoplasma"[All Fields] AND "genitalium"[All Fields]) OR "mycoplasma genitalium"[All Fields]) AND ("infertility"[MeSH Terms] OR "infertility"[All Fields])
3. ***M. gentialium* and Pregnancy Outcomes:** ("mycoplasma genitalium"[MeSH Terms] OR ("mycoplasma"[All Fields] AND "genitalium"[All Fields]) OR "mycoplasma genitalium"[All Fields]) AND (("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) OR ("pregnancy complications"[MeSH Terms] OR ("pregnancy"[All Fields] AND "complications"[All Fields]) OR "pregnancy complications"[All Fields]) OR ("pregnancy outcome"[MeSH Terms] OR ("pregnancy"[All Fields] AND "outcome"[All Fields]) OR "pregnancy outcome"[All Fields] OR ("pregnancy"[All Fields] AND "outcomes"[All Fields]) OR "pregnancy outcomes"[All Fields]))
4. ***M. gentialium* and PID:** ("mycoplasma genitalium"[MeSH Terms] OR ("mycoplasma"[All Fields] AND "genitalium"[All Fields]) OR "mycoplasma genitalium"[All Fields]) AND (("pelvic inflammatory disease"[MeSH Terms] OR ("pelvic"[All Fields] AND "inflammatory"[All Fields] AND "disease"[All Fields]) OR "pelvic inflammatory disease"[All Fields]) OR PID[All Fields] OR (("pelvis"[MeSH Terms] OR "pelvis"[All Fields] OR "pelvic"[All Fields]) AND inflection[All Fields]))

Appendix B: Quality Assessment Criteria

Source population:

- Good = women at risk of outcome
- Fair = population not defined and/or all women were symptomatic
- Poor = source population not at risk of outcome

Selection of participation:

- Good = systematic method of selection outlined, meant to reduce selection bias
- Fair = selection process not explained
- Poor = concerns about selection bias based on selection method

Exposure measurement:

- Good = well explained PCR, serology, or TMA assay methods
- Fair = concerns about ascertainment definitions or procedures
- Poor = methods proven to be flawed

Outcome measurement:

- Good = objectively defined outcome definition (PMNs, laparoscopy, etc.)
- Fair = subjectively defined outcome definition (clinically defined), or less rigorous objective definition (e.g., lower PMN counts)
- Poor = outcome definition not reported

Control for confounding:

- Good = confounding taken into account
- Fair = no control for confounding done
- Poor = inappropriate use of control for confounding

Primary or secondary analysis:

- Good = primary or secondary analysis
- Fair = not a main analysis
- Poor = no designation of “poor” for this variable

Other potential bias:

- Good = none identified (provision of test kits alone not considered potential bias)
- Fair = possible bias outlined (including receipt of funding and honoraria from diagnostics of pharmaceutical companies)
- Poor = clear bias outlined

Overall assessment:

- Good = less than three fair or poor
- Fair = three or more fair
- Poor = two or more poor

Appendix C: Quality Assessment of Included Studies

Author, year of publication and study design	Source population	Selection of participants	Strength of Exposure measurement	Strength of Outcome measurement	Control for confounding	Primary, or secondary analysis	Other potential bias detected (Possible conflict of interest)	Overall Quality Assessment
Cervicitis								
Palmer H M, 1991[23]	**Good** Genitourinary Clinic attendees, Age 16-40	**Fair** Recruitment method NR	**Good** PCR	**Fair** Clinical and microbiologic definition, moderate strength	**Fair** None	**Good** Primary	**Fair** MG detection from three separate sites (vagina, cervix, urethra), unclear connection to cervicitis	**Fair**
Uno M, 1997 [24]	**Good** Obstetric and Gynecology department attendees, Age 19-49	**Fair** Recruitment method NR	**Good** PCR	**Fair** Clinical and microbiologic definition, moderate strength	**Fair** None	**Good** Secondary	**Fair** Pregnant women as comparison group	**Fair**
Casin I, 2002 [25]	**Fair** Recruitment venue not reported, all symptomatic women	**Good** Consecutive women presenting with genital symptoms	**Good** PCR	**Fair** Microbiologic definition (≥10PMNs/HPF), moderate strength	**Fair** None	**Good** Primary	**Fair** Unusually high prevalence of cervicitis	**Fair**
Manhart 2003 [14]	**Good** STI Clinic attendees, age 16-45 with samples, previously taken samples	**Good** Randomly selected women	**Good** PCR	**Good** Clinical and microbiologic definition (≥30PMNs/HPF), strong	**Good** Age, proliferative phase of menstrual cycle, other causes of cervicitis	**Good** Primary	**Fair** Sample of previously frozen specimens	**Good**
Pepin J, 2005 [22]	**Good** Female Sex Workers attendees at FSW/STI clinics	**Fair** Recruitment method NR	**Good** PCR	**Fair** Clinical definition, moderate strength	**Good** Age, other pathogens, bleeding after sampling, inflammatory cervix, cervical motion tenderness	**Good** Primary	**Good**	**Good**
Falk L, 2005 [26]	**Good** STI Clinic attendees	**Good** All female attendees at the clinic	**Good** PCR	**Fair** Microbiologic definition(more PMNL than epithelial cells), low-moderate strength	**Fair** None	**Fair** Not a main analysis Study designed to determine signs and symptoms associated with CT and MG prevalance and rate of partner infection	**Good**	**Fair**
Anagrius C, 2005 [15]	**Good** STI Clinic attendees	**Good** Consecutive patients	**Good** PCR	**Good** Microbiologic definition (≥30PMNs/HPF), strong	**Fair** None	**Good** Primary	**Good**	**Good**
Korte J E, 2006 [27]	**Good** Minority women from previous study population, randomized controlled trial of behavioral-cognitive intervention to reduce STI recurrence	**Fair** Recruitment method NR	**Fair** PCR (possible contamination)	**Fair** Clinical definition, moderate strength	**Good** Coinfection, age, pregnancy status, and intervention group	**Good** Primary	**Good**	**Fair**
Pepin J, 2006 [16]	**Good** Attendees at nine STI clinics for vaginal discharge. Excluded women who sought STI screening, pregnant women, and those with the main complaint of lower abdominal pain, or allergic to the study drugs	**Fair** Recruitment method NR	**Good** PCR	**Good** Microbiologic definition (≥30PMNs/HPF), strong	**Good** Age, presence of other pathogens	**Good** Primary	**Good**	**Good**

Author, year of publication and study design	Source population	Selection of participants	Strength of Exposure measurement	Strength of Outcome measurement	Control for confounding	Primary, or secondary analysis	Other potential bias detected (Possible conflict of interest)	Overall Quality Assessment
Hogdahl M, 2007 [28]	**Good** STI Clinic attendees. Excluded those who had antibiotics in the previous two weeks	**Fair** Recruitment method NR	**Good** PCR	**Good** Microbiologic definition (≥30PMNs/HPF), strong	**Fair** None	**Fair** Not a main analysis Study designed to test easy-to-perform laboratory tests to predict MG infection	**Fair** Previously collected and frozen samples	**Fair**
Huppert J S, 2008 [29]	**Good** Teen health center or Emergency Department attendees, age 14-21. Heterosexual contact in last 6 months and reporting either genitourinary symptoms or a risk for STI	**Fair** Recruitment method NR	**Good** TMA	**Fair** Clinical definition, moderate strength	**Fair** None	**Good** Primary	**Fair** Receipt of research funds, test kits, and honoraria from diagnostics manufacturering company.	**Fair**
Moi H, 2009 [17]	**Good** STI Clinic attendees	**Good** All women who voluntarily attended the clinic	**Good** PCR	**Good** Microbiologic definition (>30PMNs/HPF), strong	**Fair** None	**Good** Primary	**Good**	**Good**
Gaydos C, 2009 [18]	**Good** STI Clinic attendees	**Good** Every fifth patient attending the clinic was eligible for inclusion	**Good** PCR/TMA	**Fair** Clinical Definition, moderate strength	**Good** Adjusted for CT, NG, TV, contact referral and BV	**Good** Primary	**Good** TMA Assay provided by disgnostics manufacturing company	**Good**
Falk L, 2010 [30]	**Good** STI Clinic attendees. Women attending clinic due to former or current partners' verified or suspected chlamydia infection	**Fair** Recruitment method NR	**Good** PCR	**Good** Clinical and microbiologic definition (≥30PMNs/HPF), strong	**Fair** None	**Fair** Not a main analysis Study was to test different definitions of cervicitis	**Good**	**Fair**
Lusk M J, 2011 [19]	**Good** STI Clinic attendees	**Good** Consecutive eligible consenting women	**Good** PCR	**Good** Microbiologic definition (≥30PMNs/HPF), strong	**Good** CT	**Good** Primary	**Good** Author's funding in part from pharmaceutical company scholarship	**Good**
Vandepitte J, 2012 [20]	**Good** Female Sex Workers or women employed in the Entertainment Industry	**Good** Recruited from the red-light district	**Good** PCR	**Fair** Clinical Definition, moderate strength	**Fair** None	**Good** Secondary	**Good**	**Good**
Bjartling C, 2012 [31]	**Good** Emergency Gynecologicial outpatient services attendees. Symptoms of acute or semiacute nature (including pathological symptoms of early pregnancy)	**Fair** Recruitment method NR	**Good** PCR	**Fair** Clinical and microbiologic definition (more leukocytes than epithelial cells in the absence of clue cells and/or inflammatory vaginitis), low/moderate strength	**Good** Age, CT	**Good** Primary	**Fair** All women had acute or semi-acute gynecologic symptoms	**Fair**
Mobley V L, 2012 [32]	**Good** STI Clinic attendees. English speaking, ≥18 years of age	**Fair** Recruitment method NR	**Good** TMA	**Fair** Clinical Definition, moderate strength	**Good** Age, vaginal discharge, douching, asymptomatic at presentation	**Good** Secondary	**Fair** Two authors from diagnostics manufacturing company	**Fair**
Oliphant J, 2013 [21]	**Good** STI Clinic attendees. Excluded if <16 years of age or had take antibiotics within the previous 2 weeks, were menstruating, had undergone any cervical procedure within the past month, had a hysterectomy	**Good** All women attending the clinic were eligible.	**Good** PCR	**Good** Microbiologic definition (≥30PMNs/HPF), strong	**Good** Age, ethnicity, clinic, symptoms, new sexual partner in last 3 months, cervical mucopus, cervical bleeding	**Good** Secondary	**Good**	**Good**

Author, year of publication and study design	Source population	Selection of participants	Strength of Exposure measurement	Strength of Outcome measurement	Control for confounding	Primary, or secondary analysis	Other potential bias detected (Possible conflict of interest)	Overall Quality Assessment
Female Infertility								
Moller, B R 1985 [39]	**Good** Women with history of infertility for 2 or more years referred to an out-patient clinic. Excluded if had evidence of gential-tract infections during the previous 12 months or who received antibiotics during preceding 2 weeks	**Fair** Recruitment method NR	**Good** Serology	**Good** Hysterosalpingography (HSG)	**Fair** None	**Good** Primary	**Fair** Antibody test performance unclear	**Fair**
Clausen, H F 2001 [36]	**Good** Women undergoing IVF treatment	**Fair** Recruitment method NR	**Good** Serology	**Good** HSG and laparoscopy	**Good** Age, CT antibodies	**Good** Secondary	**Good**	**Good**
Svenstrup, H F 2008 [37]	**Good** Infertile women attending an infertility clinic	**Good** Consecutively recruited	**Good** Serology/PCR	**Good** Culdoscopy/laparoscopy	**Good** Age, CT antibodies	**Good** Primary	**Fair** Two authors developed the assay for pharmaceutical company	**Good**
Haggerty C L, 2008 [38]	**Good** Women in the PEACH (PID) study, recruited in the ED, obstetrics and gynecology clinics, STD clinics and private practice in 13 states. Age 14-37	**Fair** Recruitment method NR	**Good** PCR	**Fair** Clinical definition, moderate strength	**Good** Age, race, NG, CT, self-reported infertility at baseline	**Good** Secondary	**Good**	**Good**
Grzesko, J 2009 [40]	**Good** Infertile patients hospitalized at the gynecology clinic for planned laparoscopy	**Fair** Recruitment method NR	**Good** PCR	**Good** Laparoscopy	**Fair** None	**Good** Primary	**Fair** Two authors participate in clinical research sponsored by pharmaceutical company	**Fair**
Pregnancy and Delivery Outcomes								
Labbe A-C 2002 [44]	**Good** Women living in Bissau who gave birth or aborted at Simao Mendes Hospital obstetrical ward	**Good** Invited to participate within 24 hours of delivery or abortion	**Good** PCR	**Good** Preterm Birth, Still Birth, spontaneous abortion	**Fair** None	**Good** Primary	**Fair** MG ascertained after outcome	**Good**
Manhart L, 2003 [14]	**Good** STD clinic attendees. Age 16-45, attending for a new problem	**Good** Randomly selected	**Good** PCR	**Fair** Self-reported spontaneous miscarriage (<20 weeks)	**Fair** None	**Good** Primary	**Fair** Previously collected and frozen samples	**Fair**
Oakeshott, P 2004 [45]	**Good** General practice and family planning clinic attendees, <10 weeks gestation	**Good** Consecutively collected	**Good** PCR	**Good** Miscarriage, preterm birth	**Fair** None	**Good** Secondary	**Fair** Previously collected and frozen urine samples	**Good**
Edwards, R K 2006 [51]	**Good** Labor and delivery unit attendees. Singleton pregnancies, 23-32 weeks gestation, evaluated for uterine contractions	**Fair** Recruitment method NR	**Good** PCR	**Good** Spontaneous preterm delivery (<37 weeks)	**Fair** None	**Good** Primary	**Fair** All women presented with uterine contractions	**Fair**
Kataoka S, 2006 [46]	**Good** Hospital patient attendees, singleton pregnancies at <11 weeks, after their fetuses were confirmed to have normal heartbeats	**Fair** Recruitment method NR	**Good** PCR	**Good** Preterm birth or spontaneous abortion <34 weeks	**Fair** None	**Good** Primary	**Good**	**Good**

Author, year of publication and study design	Source population	Selection of participants	Strength of Exposure measurement	Strength of Outcome measurement	Control for confounding	Primary, or secondary analysis	Other potential bias detected (Possible conflict of interest)	Overall Quality Assessment
Jurstrand M, 2007 [47]	**Good** Cases: Inpatient women at the hospital, clinically diagnosed with ectopic pregnancy Controls: Healthy pregnant women screened for rubella	**Fair** Recruitment method NR	**Good** Serology	**Good** Ectopic pregnancy: clinically assessed, laparoscopic confirmed if uncertain	**Good** Age, CT	**Good** Primary	**Good**	**Good**
Hitti J, 2010 [48]	**Good** Maternity hospital attendees, ≥12 years old, presenting with spontaneous labor	**Fair** Recruitment method NR	**Good** TMA	**Good** Preterm birth: 20-36 weeks	**Good** Maternal age, cigarette smoking, second trimester bleeding, twin gestation, prior preterm birth	**Good** Primary	**Good**	**Good**
Short V L, 2010 [49]	**Good** Participants of an early pregnancy study. Girls 14-40 who presented to an ED with varying complaints, <22 week gestation	**Fair** Recruitment method NR	**Good** PCR	**Good** Spontaneous abortion: <20 weeks	**Good** Age, history of spontaneous abortion, smoking, gestational age	**Good** Primary	**Fair** Previously collected and frozen urine samples	**Good**
Vandepitte J, 2012 [50]	**Good** Female Sex Workers or women employed in the Entertainment Industry	**Good** Recruited from the red-light district	**Good** PCR	**Fair** Women who had been pregnant but no live birth	**Good** Age, use of hormonal contraceptives, NG, *Candida* infection, HIV	**Good** Secondary	**Fair** Previously collected and frozen samples	**Good**
Pelvic Inflammatory Disease								
Lind K, 1987 [59]	**Fair** Women who fulfilled the criteria for a provisional clinical diagnosis of PID	**Fair** Recruitment method NR	**Fair** Serology (non-standard cut-off used)	**Good** Salpingitis: laparscopically or clinically defined	**Fair** None	**Good** Primary	**Fair** Serological assay and choice of titre cutoff unclear	**Fair**
Cohen C R, 2002 [57]	**Good** STD clinic attendees, Age 18-40 presented with low abdominal pain that lasted for ≤14 days	**Fair** Recruitment method NR	**Good** PCR	**Good** Endometritis: presence of at least one plasma cell per 120x microscopic field	**Fair** None	**Good** Primary	**Good**	**Good**
Simms L, 2003 [60]	**Good** Cases: from larger study of PID, Controls: women attending obstetrics and gynecology for bilateral tubal ligation	**Fair** Recruitment method NR	**Good** PCR	**Fair** PID clinically diagnosed	**Fair** None	**Good** Primary	**Good**	**Fair**
Jurstrand M, 2007 [47]	**Good** Cases: Inpatient women at a University Hospital, with clinically diagnosed PID. Controls: Healthy pregnant women screened for rubella	**Fair** Recruitment method NR	**Good** Serology	**Fair** PID clinically diagnosed	**Good** Age, CT	**Good** Primary	**Good**	**Good**
Haggerty C L, 2008 [38]	**Good** Participants of the PID evaluation and clinical health (PEACH) study. Recruited in the ED, obstetrics and gynecology clinics, STD clinic and private practices in 13 states, Age 14-37	**Fair** Recruitment method NR	**Good** PCR	**Good** Endometritis: ≥5 surface epithelium neturophils per x400 field and/or ≥2 stromal plasma cells per 120x field	**Good** Age, race, NG, CT, (cohort: self-reported partner treatment, sex between visits)	**Good** Primary	**Fair** Previously collected and frozen samples	**Good**
Bjartling C, 2010 [58]	**Good** Women seeking termination of pregnancy at outpatient service at a University Hospital. Matched cases and controls on age, month of testing, procedure used (medical or surgical)	**Fair** Recruitment method NR	**Good** PCR	**Fair** PID clinically diagnosed	**Good** Age, CT	**Good** Primary	**Good**	**Good**

Author, year of publication and study design	Source population	Selection of participants	Strength of Exposure measurement	Strength of Outcome measurement	Control for confounding	Primary, or secondary analysis	Other potential bias detected (Possible conflict of interest)	Overall Quality Assessment
Oakeshott P, 2010 [62]	**Good** Female students from 20 London universities. Age ≤27, sexually active, not pregnant, and not tested for CT in past 3 months, 12 month follow up	**Fair** Recruitment method NR	**Good** PCR	**Fair** PID clinically diagnosed	**Fair** None	**Good** Primary	**Fair** Tested stored self-obtained vaginal swabs	**Fair**
Bjartling C, 2012 [31]	**Good** Women attending the emergency gynecological outpatient services at a university hospital. Cases and controls matched on age and month of visit.	**Fair** Recruitment method NR	**Good** PCR	**Fair** PID clinically diagnosed	**Good** Age, CT	**Good** Primary	**Fair** All women had some sort of acute or semiacute gynecological symptoms	**Fair**
Taylor-Robinson D, 2012 [61]	**Good** Women with lower abdominal pain that had been seen initially in 1990	**Good** Selected sequentially	**Good** PCR/serology	**Good** Salpingitis: confirmed through laparoscopy	**Fair** None	**Fair** Not a main analysis Study to evaluate the microbiologic causes of individual disease, not overall association with MG	**Fair** Previously collected and frozen samples	**Fair**
Vandepitte J, 2012 [20]	**Good** Women who engaged in sex work and/or were employed in entertainment facilities	**Good** Recruited from the red-light areas in southern Kampala	**Good** PCR	**Fair** PID clinically diagnosed	**Fair** None	**Good** Primary	**Good**	**Good**

Abbreviations: ND = Not Done, OR = Odds Ratio, PR =Prevalence Ratio, AOR = Adjusted Odds Ratio, APR =Adjusted Prevalence Ratio, CI = confidence interval, MG = *Mycoplasma genitalium*, CT = *Chlamydia trachomatis*, NG = *Neisseria gonorrhoeae*, TV = *Trichomonas vaginalis*, BV = Bacterial vaginosis, TMA = transcription-mediated amplification assay, PCR = polymerase chain reaction, STI = Sexually transmitted infection, PMNs or PMNL = polymorphonuclear leucocytes, HPF = high-power microscopic field, TFI = Tubal Factor Infertility

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