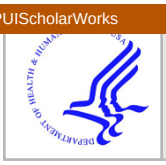

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Sexually Transmitted Diseases and Infertility

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Abstract

Female infertility, including tubal factor infertility, is a major public health concern worldwide. Most cases of tubal factor infertility are attributable to untreated sexually transmitted diseases that ascend along the reproductive tract and are capable of causing tubal inflammation, damage, and scarring. Evidence has consistently demonstrated the effects of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* as pathogenic bacteria involved in reproductive tract morbidities including tubal factor infertility and pelvic inflammatory disease. There is limited evidence in the medical literature that other sexually transmitted organisms, including *Mycoplasma genitalium*, *Trichomonas vaginalis*, and other microorganisms within the vaginal microbiome may be important factors involved in the pathology of infertility. Further investigation into the vaginal microbiome and other potential pathogens is necessary in order to identify preventable causes of tubal factor infertility. Improved clinical screening and prevention of ascending infection may provide a solution to the persistent burden of infertility.

Overview

Infertility, which is defined as the inability to conceive after 12 months or longer of regular unprotected sexual intercourse, is a common public health concern worldwide. Globally, 9% of reproductive-aged women, including nearly 1.5 million women in the United States, are infertile (1, 2). The burden of infertility is inordinately higher among women in developing

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Condensation

There is evidence that *Chlamydia trachomatis* and *Neisseria gonorrhoeae* can cause tubal factor infertility; however, additional pathogens also may be important factors.

countries; in some of regions of South and Central Asia, sub-Saharan and Northern Africa, the Middle East, and Eastern Europe, infertility rates can reach up to 30% in reproductive-aged women (3). The inability to conceive not only creates a considerable cost burden for patients and the healthcare system but is also a major psychological stressor for millions of couples (4). In several areas of the world, especially in low- and middle-income countries where having biological children is highly valued and expected of couples, involuntary infertility can lead to stigmatization, economic deprivation, social isolation and loss of status, public shame and humiliation, and in some cases, violence (5, 6). Female infertility may be attributed to a number of factors, typically divided into endocrine, vaginal, cervical, uterine, tubal, and pelvic-peritoneal factors, and although estimates vary, approximately 15-30% of cases still remain unexplained (7). Further insight into the causes of infertility is necessary to help alleviate this multifactorial burden on society.

Tubal factor infertility (TFI) ranks among the most common causes of infertility, accounting for 30% of female infertility in the United States and is even more prevalent in certain communities (8). Paralleling the aforementioned global infertility disparity, TFI is disproportionately common in women in developing countries; for example, it has been shown to account for over 85% of female infertility cases in regions of sub-Saharan Africa compared to 33% of cases worldwide (3). Most cases of TFI are due to salpingitis, an inflammation of the epithelial surfaces of the fallopian tubes, and subsequent pelvic-peritoneal adhesions, both of which are mostly caused by previous or persistent infections (9, 10) Bacteria ascend along mucosal surfaces from the cervix to the endometrium and ultimately to the fallopian tubes. This causal pathway presents itself clinically as acute pelvic inflammatory disease (PID), which in turn is strongly associated with subsequent TFI. In fact, approximately 15% of women with PID develop TFI, and the number of episodes of PID a woman experiences is directly proportional to her risk of infertility (11, 12). However, the majority of women with TFI do not have a history of clinically-diagnosed acute PID, but rather develop asymptomatic or minimally-symptomatic salpingitis as a result of upper genital tract infection (9, 13). Examining the effect of those infections, particularly those that occur in the absence of clinically-evident PID, is critical to understanding TFI.

Several sexually transmitted diseases (STDs), including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, have been widely studied to understand their role in salpingitis and infertility. Additionally, several other pathogens such as *Mycoplasma genitalium*, *Trichomonas vaginalis,* and other microorganisms within the vaginal microbiome may also play roles in tubal damage and other potential causes of infertility. Still, data suggest that not all infections yield the same long-term sequelae. The roles of different STD pathogens, co-infections, and interactions with host characteristics, including their individual vaginal microbiome, may all affect a woman's subsequent ability to conceive. While screening and treatment efforts for *C. trachomatis* and *N. gonorrhoeae* have been developed to reduce the incidence of PID and subsequent TFI, additional data is needed to determine the role of other potential pathogens and whether early detection can prevent tubal damage. In this paper, we discuss the pathogens *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium*, *T. vaginalis*, and other potential organisms that may affect female fertility, and we address the clinical importance of screening and preventing the spread of those infections.

Methodology

We conducted a comprehensive literature search to identify articles by using the electronic databases Medline, Embase, Web of Science, and CINAHL, in addition to scrutinizing references of identified articles. Within each database, we combined the term “female infertility” with four different infection terms: “*Chlamydia trachomatis*,” “*Neisseria gonorrhoeae*,” “*Mycoplasma genitalium*,” and “*Trichomonas vaginalis*.” Within the Medline database, we refined the search by excluding the MeSH headings unrelated to female infertility and at least one of the four organisms. Within the Embase search, we used Emtree to identify terms, and used both “female infertility” and “uterine tube occlusion” as focused search terms to combine with each infection. We filtered results to only include articles published in English after 1975 until April 2016. Additional relevant articles were identified from bibliographies and by the recommendation of medical experts. The inclusion of the articles used in the analysis was based on quality of the study and relevance to this review: studies were excluded if they were conducted with few participants, had no comparison group, or constituted of case reports. Studies that did not report sufficient data to determine the association with female infertility or reproductive morbidities were excluded for lack of relevance to the topic of review.

Chlamydia trachomatis and *Neisseria gonorrhoeae*

C. trachomatis and *N. gonorrhoeae* have been extensively shown to be associated with infertility, particularly by causing tubal inflammation. In fact, early speculation regarding the effect of *N. gonorrhoeae* on female fertility dates back to the 1870s, when the German-born gynecologist Emil Noeggarath published his revolutionary claims about gonorrhea as a clinical condition in his book *Latent Gonorrhoea in the Female Sex* (14). Though he may have widely overestimated its repercussions (postulating that gonorrhea causes 90% of female infertility), his theories eventually sparked the initiation of further investigations (15). When the bacterium *N. gonorrhoeae* was finally isolated, Noeggarath's controversial claims regarding the persistence of this “venereal poison” in the reproductive organs and its pathologic consequences were reexamined (16). Studies conducted more than a century later have since demonstrated the impact of *C. trachomatis* and *N. gonorrhoeae* on subsequent infertility.

Chlamydia trachomatis, the most common reportable disease in the United States, affects nearly 1.5 million US citizens annually (17). Unfortunately, however, because *C. trachomatis* infections are asymptomatic in most women (18, 19), infections are often unnoticed, untreated, and under-reported. For almost 40 years, evidence has shown that untreated ascending *C. trachomatis* infection can lead to irrevocable damage in the fallopian tubes including proximal and distal tubal occlusions leading to infertility (39). The increased amount of heat shock protein (hsp60) synthesized by *C. trachomatis* induces a proinflammatory immune response in the human fallopian tube epithelia, resulting in scarring and tubal occlusion (9, 20, 21). A number of seroepidemiological studies have examined the prevalence of antibodies to *C. trachomatis* and chlamydial hsp60 in women with laparoscopically- or hysterosalpingographically-confirmed fallopian tube damage and ectopic pregnancies (22-28),, indicating that history of *C. trachomatis* infection is associated

with a significantly increased risk of tubal infertility in women, regardless of the infection invoking clinical symptoms (20, 25, 29-32). Extensive research has also shown that *C. trachomatis* infection can cause PID, which often precedes infertility in women. Today, *C. trachomatis* accounts for approximately 50% of cases of acute PID in developed countries (33). Among PID patients, those with prior *C. trachomatis* infection have been shown to be more likely to experience subsequent infertility than those without a history of *C. trachomatis* infection (32-35).

While *C. trachomatis* seropositivity has long been shown to influence fallopian tube patency (36), the use of a newer, more sensitive and specific anti-CT assay by Geisler and coworkers anti-CT assay has only recently been shown to hold promise as a measure of tubal function (37, 38). In one cohort study of 1,250 infertile women with documented tubal patency undergoing fertility treatment, *C. trachomatis* seropositivity using the antibody subclasses IgG1 and IgG3 was tested (39). Results showed that of these two antibody subclasses tested, seropositivity to *C. trachomatis* based on IgG3 detection was a strong predictor of both failure to conceive and ectopic pregnancy outcomes. Because IgG3 has been shown to be involved in early inflammatory response to infection (40), the detection of IgG3 in these women may reflect that either *C. trachomatis* infection has recently cleared or indicate a persisting infection, contributing to fallopian tube damage while perhaps not yet leading to blockage of the fallopian tubes (39).

In another study of subfertile women with no visible tubal pathology, chlamydial antibody testing was associated with a 33% lower spontaneous pregnancy rate than those without chlamydial antibodies (39, 41). Coppus and colleagues suggest that these low pregnancy rates may not only be caused by the known mechanism of chronic inflammatory response causing fallopian tube damage; persistent *C. trachomatis* infections have also been shown to elicit an autoimmune response to human heat shock proteins, which may elevate the risk for impaired embryo development and implantation (41-43). Chlamydial antibody testing may therefore continue to become a valuable predictor of not only tubal patency, but also of ectopic pregnancy, intrauterine insemination failure, and embryo and pregnancy wastage, independent of tubal damage.

Although less prevalent than *C. trachomatis* in the United States, gonorrhea is still the second most common reportable disease in the United States (17). *N. gonorrhoeae* infections are also often asymptomatic among women, but as Noeggarath suspected in the 1870s, the bacterium is capable of ascending to the upper genital tract and causing severe reproductive morbidities. In particular, *N. gonorrhoeae* attacks the epithelial cells of the fallopian tube, both initially by attaching to the nonciliated mucosal cells and by sloughing off ciliated mucosal cells (9). The resulting damage hinders the fallopian tubes' ability to transport the ovum for fertilization within the tubes and implantation in the uterus, thus ultimately elevating the risk of infertility and ectopic pregnancy.

Several seroepidemiological studies have demonstrated the pathogen's effects on fallopian tube damage and subsequent infertility (44-48). Throughout those studies, women with laparoscopically- and hysterosalpingographically-confirmed TFI have consistently been shown to have a significantly higher prevalence of serologically-confirmed *N. gonorrhoeae*

infection than women with normal fallopian tubes. Like chlamydial PID, gonococcal PID has been shown to be an important cause of fallopian tube damage, greatly increasing a woman's risk of TFI. Ten to 19% of women with cervical *N. gonorrhoeae* infections have clinical signs of acute PID (50) and in regions of the U.S. with high endemic rates of gonorrhea during the 1970s and 1980s, gonorrhea was found in more than 40-50% of patients with PID (51). In recent studies, the bacteria have been identified in approximately 20% of women diagnosed with acute PID, suggesting that *N. gonorrrhoae* is not as frequent a cause of acute PID as it had been in the past (52, 53). Still, the impact of both chlamydial and gonococcal infections on the fallopian tubes currently make these pathogens the most important known preventable causes of infertility, and improving screening programs for these prevalent and commonly asymptomatic pathogens may therefore make a critical impact in the prevention of tubal pathology and infertility.

Mycoplasma genitalium

While *N. gonorrhoeae* and *C. trachomatis* are known to be pathogens in salpingitis and tubal infertility, in many cases, neither organism is identified (52). *Mycoplasma genitalium*, a member of the *Mollicutes* class with the smallest known genome of any free-living organism (54), was discovered in 1981 when it was first isolated from men with non-gonococcal urethritis (55). After the development of nucleic acid amplification assays in the early 1990s facilitating its detection, *M. genitalium* has since been shown to be a common sexually transmitted organism. (56). In the United States in 2007, the prevalence of *M. genitalium* in young adults was 1%, placing it between *N. gonorrhoeae* (0.4%) and *C. trachomatis* (2.3%) infections, and it has been detected in 15-20% of high-risk, sexually active women in the United States (57-59).

Since its discovery, numerous studies demonstrate that *M. genitalium* is strongly associated with male urethritis. In an analysis of 34 studies published between 1993-2011 studying men with non-gonococcal urethritis, 13% of 7123 men tested positive for *M. genitalium*, and several studies have demonstrated that *M. genitalium* can cause persistent or recurrent urethritis (60). After the initial findings of *M. genitalium* demonstrating its effects in males, investigators soon began to look at its effects on the female reproductive tract. While there are fewer studies in women, *M. genitalium* has been investigated to evaluate its association with several morbidities in women, including cervicitis, urethritis, PID, ectopic pregnancy, and TFI (60).

Four serological studies have investigated the relationship between past *M. genitalium* infection in women and tubal infertility (23, 24, 61, 62). Two of those studies have demonstrated a significant correlation between presence of antibodies against *M. genitalium* and laparoscopically-confirmed TFI, independent of *C. trachomatis* seropositivity (23, 24). According to Svenstrup and colleagues, among women with TFI, 23% had antibodies to *C. trachomatis* and 17% to *M. genitalium*; whereas 15% and 4% of infertile women with normal fallopian tubes had antibodies to each, respectively (24). Though not quite as high as the prevalence of antibodies to *C. trachomatis*, prior *M. genitalium* infection is thought to be an independent risk factor for tubal factor infertility. In a similar study by Clausen and colleagues, serological analyses of women with TFI reinforced the finding that *M.*

genitalium is independently associated with tubal inflammation leading to infertility (23). A more recent study by Idahl and colleagues examined the association between *M. genitalium* antibodies and infertility in 239 women diagnosed with infertility of various causes, including laparoscopically- and hysterosalpingographically-confirmed TFI, compared to 244 fertile controls (61). The results indicate that *M. genitalium* serum antibodies are more common among women with all causes of infertility (5.4%) than in fertile controls (1.6%). Among the infertile women in that sample diagnosed specifically with TFI, 9.1% were seropositive for *M. genitalium* compared with 4.6% of the fertile controls, although the association between TFI and *M. genitalium* was not statistically significant after adjusting for *C. trachomatis* seropositivity (61).

Supporting evidence has shown an association between infection with *M. genitalium* at the time of infertility evaluation and laparoscopically-confirmed tubal infertility, rather than serologically investigating past infection history. In a study comparing infertile and fertile women by polymerase chain reaction testing of cervical samples, *M. genitalium* was detected more frequently in infertile women (19.6%) compared to fertile women (4.4%) (63). However, in the study by Svenstrup and colleagues that examined the relationship between *M. genitalium* seropositivity and TFI, none of the women had a cervical swab specimen indicating current *M. genitalium* infection, and only one was positive for *C. trachomatis* (24). There does not appear to be a role for screening for *M. genitalium* infection at the time of infertility evaluation.

Several other studies, though not directly addressing fertility rates, have investigated the effects that *M. genitalium* may have on tubal inflammation, damage, and occlusion. The mechanism by which *M. genitalium* may cause the tubal scarring that leads to infertility has been studied through several *in vitro* models. McGowin and colleagues demonstrated that the organism can attach to reproductive tract epithelial cells and elicits cellular immune responses that result in inflammation (65, 66). In another *in vitro* organ culture model, *M. genitalium* adhered to human fallopian tube epithelium after experimental inoculation, causing swelling of the cilia and detachment of cilia from the epithelium (67). Svenstrup and colleagues also investigated whether mobile sperm could serve as a vector for transmitting *M. genitalium* to the upper genital tract of women, demonstrating that the organism does adhere to human spermatozoa and could be transported by sperm to the uterus and fallopian tubes to colonize and destroy the ciliated epithelia (68).

When compared with the more severe damage that *C. trachomatis* and *N. gonorrhoeae* infection create in the fallopian tube, the damage caused by *M. genitalium* tends to be moderate (65). However, when left untreated, damage may accumulate and yield serious long-term sequelae on fallopian tube function. Additionally, simultaneous infection with *M. genitalium* and other sexually transmitted bacteria may cause even more severe tubal pathology. One study conducted in Saudi Arabia used PCR performed on tubal samples from women with ectopic pregnancy and compared them to samples from fertile women undergoing partial sapingectomy for sterilization or at the time of hysterectomy (69). They found a 6-fold higher rate of infection with *C. trachomatis* and *M. genitalium* in women with ectopic pregnancy compared to the controls. There was also a higher rate of other infections, including U. urealyticum/parvum, G. vaginalis, N. gonorrhoeae, and *T. vaginalis,* but these

associations were not statistically significant. The investigators noted that co-infection with at least 2 organisms led to a 5-fold increase in the risk of ectopic pregnancy, providing further evidence that multiple infections leads to greater risk of tubal damage (69).

Animal studies have also been performed to investigate the potential role of *M. genitalium* on tubal scarring and inflammation. Female grivet monkeys and marmosets inoculated with *M. genitalium* developed severe endosalpingitis, along with luminal exudates and adhesions between mucosal folds in the fallopian tubes, similar to changes induced by chlamydial infection (70). Additionally, female Swiss Webster mice developed upper reproductive tract infection as early as 3 days after being inoculated with *M. genitalium*, showing experimentally that *M. genitalium* is capable not only of ascending through the upper genital tract, but persistently colonizing reproductive tract tissues that could lead to long-term tubal inflammation and occlusion (71).

Both serological and epidemiological studies have explored whether *M. genitalium* is associated with clinical PID and salpingitis. In an analysis of 193 patients with clinically-diagnosed PID and 246 healthy pregnant controls, 17% were *M. genitalium* seropositive, although the association was not statistically significant after adjusting for age and presence of antibodies to *C. trachomatis* (72). An older study by Møller and colleagues also showed an association; in a group of patients with acute PID without *C. trachomatis* antibodies, almost 40% had a four-fold or greater change in the titre of *Mycoplasma genitalium* antibodies (73). Still, results are conflicting, as Lind and colleagues assessed the significance of antibodies to *M. genitalium* in patients with acute salpingitis and failed to confirm any association (74).

Recent studies have examined the relationship between current cervical or endometrial *M. genitalium* infection and upper genital tract infection (74-78). In an analysis of 586 women who participated in the PID Evaluation and Clinical Health (PEACH) Study, a randomized multicenter clinical trial in the United States, 31% of women who tested positive for *M. genitalium* in the endometrium reported recurrent PID, 42% had chronic pelvic pain, and 22% were infertile (75). However, a large prospective trial of 2378 young women in London failed to show an association between *M. genitalium* and acute PID. Among women with *M. genitalium* at baseline, 3.9% developed PID after 12 months compared with 1.7% of women without baseline infection; however, this difference was not statistically significant (66). Oakeshott and colleagues concluded that because the population attributable risk of PID due to *M. genitalium* was only 4%, *M. genitalium* infection is not an important risk factor for pelvic inflammation (79). This particular European population may not be generalizable to populations with higher prevalence rates of *M. genitalium* infection, where, if confirmed, this two-fold increased risk of PID due to *M. genitalium* infection could constitute a major public health problem (75). Still, while evidence shows that *M. genitalium* is often present in or associated with PID cases, more data is necessary to determine the role of this microorganism in the pathogenesis of PID and subsequent TFI.

M. genitalium may not only affect tubal patency; several studies have investigated its effects on pregnancy outcomes such as ectopic pregnancy, recurrent pregnancy loss, and preterm birth. However, unlike for *C. trachomatis,* there is limited evidence that the pathogen is

associated with these adverse pregnancy outcomes. A serological case-control study by Jurstrand and coworkers showed no significant correlation between *M. genitalium* antibodies and ectopic pregnancy (80). According to a recent meta-analysis, *M. genitalium* infection has been shown to be significantly associated with increased risk of both spontaneous abortion and preterm birth in some studies, although evidence is inconsistent (81). While data is emerging on the impact of *M. genitalium* on the reproductive health of women, further research is necessary to solidify any conclusions regarding *M. genitalium* and adverse pregnancy outcomes.

Trichomonas vaginalis

Like that of *M. genitalium,* the role of *Trichomonas vaginalis* infection in reproductive tract pathology has been understudied, but investigators have shown that it may be associated with female infertility. *T. vaginalis* is the most common non-viral, sexually transmitted pathogen in the United States. According to the World Health Organization, the protozoan *T. vaginalis* accounts for more than half of all curable STDs worldwide (82). An estimated 7.4 million new infections occur annually in the U.S. (83) and approximately 3.1% of reproductive-age women are infected (84). Given the high prevalence of *T. vaginalis* in the population, any potential impact of the organism on the upper reproductive tract could constitute a serious public health concern.

Data associating *T. vaginalis* with TFI and pelvic inflammation in the literature is relatively weak. Few retrospective studies have found that women with self-reported infertility were 2-3 times more likely to have a current *T. vaginalis* infection, and women with a self-reported history of a *T. vaginalis* infection have approximately a two-fold risk of tubal infertility (45, 84-88). Additionally, a trend exists between increasing number of episodes of *T. vaginalis* infection and increasing risk of infertility (45). However, many of the epidemiologic studies analyzing the association between trichomoniasis and infertility failed to control for important confounding variables such as presence or history of other reproductive tract infections.

Upon investigation of endometrial inflammatory changes elicited by infections, immunohistochemical evidence shows that *T. vaginalis* may contribute to upper genital tract inflammation (89). Pathologically, *T. vaginalis* has been shown to be capable of ascending the upper genital tract and has been associated with up to 30% of acute salpingitis cases, although within the same study, trichomonads were not demonstrated in tubal cultures from cases of salpingitis (90). *T. vaginalis* has been shown to be associated clinically with endometritis, salpingitis, and atypical PID (91-94), demonstrating that it may be an important pathogen in upper genital tract damage. Other potential mechanisms linking *T. vaginalis* infection to infertility include disruption of sperm motility (93), phagocytosis of sperm, and transportation of other infectious agents to the upper genital tract by motile trichomonads (86, 87), although these mechanisms do not directly affect the female reproductive tract.

Co-infection of *T. vaginalis* and *C. trachomatis* may increase the risk of upper genital tract infection more than the risk of *C. trachomatis* infection alone, and women with both *T. vaginalis* and HIV-1 have been shown to have a significantly higher risk of PID than women

without *T. vaginalis* (87, 94). Because trichomonads are capable of phagocytizing bacteria, yeast, vaginal epithelial cells, mycoplasmas, and herpesviruses *in vitro* (96-99), investigators speculate that *T. vaginalis* infection may be capable of spreading other pathogens throughout the upper genital tract, thereby indirectly eliciting tubal damage and infertility. Moreover, despite some of these weak associations, proposed mechanisms, and possible co-infection risks, there is currently no strong conclusive evidence regarding the causative effects of *T. vaginalis* on PID or infertility.

Vaginal Microbiome and Other Potential Pathogens

N. gonorrhoeae, C. trachomatis, and M. genitalium may not be the only organisms capable of damaging the reproductive tract. Both *Mycoplasma hominis* and *Ureaplasma urealyticum*, two common species of genital mycoplasma, have been investigated as possible causative agents for infertility and pelvic inflammation. *M. hominis* is commonly found in the upper genital tract. The adverse influence of *M. hominis* on the female reproductive tract was identified in 1976 by Mårdh and colleagues, as they demonstrated with *in vitro* organ cultures the swelling of the ciliated tubal epithelial cells due to *M. hominis* infection (100). The organism has been isolated from the fallopian tubes of women with a history of infertility and laparoscopically-confirmed salpingitis, although recent data have not necessarily reproduced these findings (62, 90, 101, 102).

Ureaplasmas, including *U. urealyticum,* have also been investigated as potential culprits of female infertility. Like *M. hominis*, ureaplasmas have been isolated from the fallopian tubes of patients with PID, yet their presence in patients with PID is rare (90, 103). Some studies suggest a causal relationship between *U. urealyticum* and infertility, but most controlled studies do not confirm such a pathogenic role. Evidence supporting both *M. hominis* and *U. urealyticum* as agents involved in infertility is not nearly as conclusive as existing evidence for pathogens such as *C. trachomatis* and *N. gonorrhoeae*; while some investigators have been able to detect each of the organisms in infertile patients and in patients with upper genital tract disorders, several have not shown any correlation (103-106). As with *T. vaginalis*, the existing evidence for *M. hominis* and ureaplasmas as pathogens causing infertility is therefore not sufficiently definitive.

While the focus of this review was to identify sexually transmitted pathogens that affect fertility, other infectious diseases are important to consider in discussing infertility. In the developing world where exposure to *Mycobacertium tuberculosis* is common, genital tuberculosis (GTB) is a significant cause of infertility. Though its incidence is less than 1% in industrialized countries, GTB rates can be as high as 13% in developing countries, eliciting a major public health concern (107). In almost all cases of GTB, *Mycobacertium tuberculosis* spreads hematogenously from a primary source, most commonly the lungs, to the fallopian tubes, producing irreversible tubal damage and ultimately leading to TFI in up to 40% of cases (1). In addition to infertility, GTB has also been shown to be an important risk factor for ectopic pregnancy in developing countries (108, 109). The silent nature of GTB, which often persists without any clinical manifestations, allows development of fulminating infection without detection (110). Early detection and treatment of GTB is vital

to improve reproductive outcomes, but unfortunately provides no benefit to reverse tubal damage once the disease is advanced (111).

Rather than a single organism impairing female fertility, variations in the overall vaginal microbiome, such as in bacterial vaginosis, may also have a role in infertility (112). A recent meta-analysis exploring the role of bacterial vaginosis (BV) on infertility has shown that BV is significantly more prevalent in infertile women than in pregnant women of the same population (113). According to this systematic review of 12 studies reporting the prevalence of BV in patients with infertility of all subtypes, an estimated one in five infertile women has BV, and at least one in three has an abnormal vaginal microflora. Four studies have shown that BV is significantly more prevalent in women with tubal infertility than in women with non-tubal infertility (114-117), including a recent study among Nigerian women that demonstrated that BV was four times more prevalent in women with TFI compared to fertile controls (117). Additionally, after adjusting for several factors, including current infection with *N. gonorrhoeae, C. trachomatis*, or *T. vaginalis*, BV has been linked to laparoscopically-confirmed PID, endometritis, and salpingitis (114, 118-121), suggesting that the effects of BV are not confined to the lower genital tract and may therefore interfere with female fertility. In fact, microorganisms that are highly prevalent in the vagina among women with BV have been recovered in the fallopian tubes of women with laparoscopically-confirmed PID and acute salpingitis (122).

However, the role of BV in infertility and in upper genital tract morbidity is still not completely clear, as other studies refute any significant correlation (123). Likewise, the studies that do show correlations between BV and tubal pathology do not necessarily help distinguish whether this finding is secondary to previous tubal damage caused by infections such as *C. trachomatis* and *N. gonorrhoeae,* or whether BV infection may help spread these infections to the upper genital tract (116). It is uncertain whether or not BV itself is the direct cause of damage on the fallopian tubes, but given its high prevalence among women with TFI, alongside the high percentage of women with BV that remain undiagnosed and untreated, further investigations elucidating the role of anaerobic overgrowth, biofilms, and the vaginal microbiome are needed (117).

Conclusions

In summary, the totality of the evidence linking *N. gonorrhoeae* and *C. trachomatis* to infertility is compelling. However, the associations found between *M. genitalium*, *T. vaginalis* and other potential pathogens are suggestive, but far from definitive. Additional research is necessary to strengthen the suggestions that *M. genitalium* and *T. vaginalis* can cause infertility. We would recommend additional serological studies in a diverse sample of reproductive age women while controlling for the history of other STDs. Prospective studies assessing demographic and behavioral factors, the impacts of co-infections, and the impact of the vaginal microbiome are needed to sort out the relationship between these pathogens and impaired fertility and adverse pregnancy outcomes.

Nonetheless, for those pathogens where reproductive tract pathology is evident, screening and treatment should be emphasized in the clinical setting. The literature regarding the

importance and benefit of treating these pathogens to enhance fertility on the population level is sparse, although a recent study in Washington observed a potential association between disease management trends and reduction of reproductive morbidities (53). While further investigations are necessary to establish a tangible benefit, it is nonetheless well-understood that women who delay seeking care for what is often an asymptomatic infection have a higher risk for infertility and other reproductive morbidities. The U. S. Preventive Services Task Force has issued chlamydia and gonorrhea screening recommendations since 2000 to reduce associated morbidities (124), but such guidelines regarding other non-traditional pathogens have not been established. Future research to evaluate the impact of screening and treatment programs for non-traditional pathogens such as *Mycoplasma genitalium* and other organisms in the microbiome should be considered to help guide clinical practice and health policy to more effectively reduce the global burden of infertility.

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