An overview regarding the relationship between Mollicutes, infertility and antibiotic resistance (Review)

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Abstract. Throughout the past decades, physicians have increasingly conferred regarding the role of Mollicutes in infertility in both male and female patients. Although *Ureaplasma* and *Mycoplasma* do not represent a leading cause of infertility, whether dermatovenerologists, gynecologists and urologists should not disregard them when screening patients with infertility problems is discussed in the present review. While these infections are completely asymptomatic in ~80% of cases, they do lead to both chronic inflammation of the genital tract and reproductive disorders. Different Mollicute strains and/or serovars, genomic traits and proteomic markers have been examined in order to understand not only the exact mechanism by which they cause infertility, but also their relationship with the worldwide spreading resistance to antibiotics. The current review provided an overview of the latest studies regarding the new findings on the relationship between Mollicutes, infertility and antibiotic resistance. Awareness should be raised among clinicians to screen sexually active adults wishing to conceive who have failed to achieve a pregnancy; in addition, an antibiogram should be performed and treatment should be carried out according to the guidelines.

Contents

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1. Introduction

The World Health Organization (WHO) defines clinical infertility as a condition of the reproductive system characterized by 'the inability to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse', in the absence of any contraceptive methods (1). This condition, affecting one in seven couples, can be attributed to factors related to either the female, the male or both partners (1,2). The current paper does not cover any organic, hormonal or other external causes of infertility; the authors only scrutinized the infectious trigger. Even though Mollicutes (*Ureaplasma* and *Mycoplasma*) are typically considered harmless colonizers of the male and female reproductive tracts, recent evidence points towards their potential as sexually transmitted opportunistic pathogens, which may lead to chronic asymptomatic disorders that affect fertility in both genders. In men, *Ureaplasma* is related to conditions such as urethritis, prostatitis, epididymitis and infertility. Studies have shown that both *Ureaplasma* and *Mycoplasma hominis* can negatively impact sperm quality (1,2). Reproductive tract infections can induce leukocytosis in semen, trigger the release of inflammatory factors and disrupt levels of reactive oxygen species (ROS), potentially resulting in vas deferens obstruction and subsequent infertility in men (1,3). On the other hand, *Ureaplasma* and *Mycoplasma hominis* in women can contribute to various conditions, such as acute urethritis, bacterial vaginosis, pelvic inflammatory disease and tubal infertility (2,4).

Furthermore, asymptomatic infections caused by these microorganisms may provoke pro-inflammatory immune responses in the endometrium, potentially affecting pregnancy outcomes (2). Sexually transmitted infections can impair fertility through direct damage to reproductive organs and gametes, as well as through inflammation-induced tissue damage, scarring and obstruction. Furthermore, infection-related genital inflammation can disrupt the natural immunomodulation process in the female genital tract, crucial for facilitating fertilization, embryo implantation and a successful pregnancy (5). The prevalence of *Ureaplasma* and *Mycoplasma hominis* in the urogenital tracts of infertile individuals varies significantly across regions, countries and demographic groups based on factors such as age, ethnicity and socioeconomic status. While numerous studies have been conducted in the past decade, comprehensive data from

large cross-sectional studies remain limited (5). Likewise, an important aspect to consider is that only chronic infections with Mollicutes can cause infertility. Therefore, we should ponder upon the relationship between the microorganisms and the antibiotics used to treat the disease; there appears to be a global trend for Mollicutes to become increasingly resistant to classic antibiotics, hence making infectious causes of infertility a severe public health issue (6).

The aim of the present study was to emphasize the importance of screening and treating genital infections caused by Mollicutes. If left untreated, these infections can lead to severe complications, including infertility, a condition that has emerged as a significant global health matter. By highlighting the critical need for early detection and appropriate medical intervention, the present study endeavors to address the broader implications of Mollicutes infections on reproductive health and contribute to the ongoing efforts to mitigate infertility rates worldwide.

2. Mollicutes

Types of bacteria. Ureaplasmas and Mycoplasmas, members of the Mollicutes class and the Mycoplasmataceae family, use urea as a metabolic substrate for ATP generation (7,8). These microorganisms, like others in their class, are obligate parasites of eukaryotes; they lack a cell wall, employ a non-standard genetic code, possess small genomes and depend on cholesterol. Among the five human pathogenic species in the Mollicutes class, *Mycoplasma pneumoniae* is a well-known respiratory pathogen causing 'walking pneumonia'. The other four species, *Mycoplasma genitalium*, *Ureaplasma parvum*, *Ureaplasma urealyticum* and *Mycoplasma hominis*, all constitute urogenital pathogens. Ureaplasmas and Mycoplasmas are among the smallest self-replicating organisms capable of existing freely outside of cells. This genus comprises seven recognized species isolated from humans and various animals (9). Phylogenetic analysis has classified *Ureaplasma* into two species: *Ureaplasma parvum* and *Ureaplasma urealyticum*. Most human *Ureaplasma* isolates belong to *Ureaplasma parvum* (biovar 1), associated with the majority genital tract infections, while *Ureaplasma urealyticum* (biovar 2) is less commonly isolated (10). Despite this distinction, studies regarding male infertility often discuss the role of Ureaplasmas without differentiation (1). Up to now, at least 14 serovars have been identified: *Ureaplasma urealyticum* includes 10 serovars-UUR2, UUR4, UUR5 and UUR7-13, while *Ureaplasma parvum* only includes four-UPA1, UPA3, UPA6 and UPA14 (9).

Pathogenic mechanisms. These Mollicutes can attach to various cell types, including the urethral epithelial cells, spermatozoa and even erythrocytes. The exact adhesion mechanism of the Ureaplasmas has remained to be fully elucidated; however, existing evidence suggests that the receptors are sialyl residues and/or sulfated compounds. An important family of surface proteins, namely the multiple-banded antigens (MBA), is immunogenic during *Ureaplasma* infections. MBAs have been used as a basis to develop reagents for diagnostic purposes and serotyping (9).

Although Ureaplasmas do not produce toxins, they do possess potential virulence factors. Immunoglobulin A protease contributes to the pathogenic potential of Ureaplasmas by helping to evade host defenses (9). Studies conducted in a health center in Iran have shown higher prevalence rates of *Mycoplasma hominis* and *Ureaplasma urealyticum* in infertile females (4.28%) compared to fertile individuals (3.14%), potentially linked to hormonal disorders affecting immunity levels and bacterial colonization (11). In addition, Ureaplasmas possess phospholipase A1, A2 and C activities, which may impact prostaglandin synthesis by production of free arachidonic acid, potentially inducing premature labor. An intact humoral immune response is crucial for limiting *Ureaplasma* invasion beyond mucosal surfaces (9).

Related diseases and the relationship with infertility. Ureaplasmas represent a fragment of the normal commensal flora in the human genital tract, with colonization rates ranging from 60 to 80% globally. While generally harmless, Ureaplasmas have been linked to various clinical conditions, including non-gonococcal urethritis, pelvic inflammatory disease, infertility, adverse pregnancy outcomes and neonatal respiratory issues due to vertical transmission (2,4). The colonization of the male and female mucosal surfaces in the urogenital tracts, as well as of the neonatal respiratory tract, with *Ureaplasma parvum* is more common than that with *Ureaplasma urealyticum*.

In infertile men, the detection rate of *Ureaplasma urealyticum* in semen is oftentimes higher (5-58%) than in fertile men (3-31%), with unclear mechanisms of infertility. However, the role of *Ureaplasma urealyticum* in reducing sperm motility at low pH and increasing sperm velocity at high pH is well known (3). *Mycoplasma* infections have been associated with reduced sperm agglutination, viability and DNA damage, causing reduced sperm counts (12). Almost 80% of the infected patients, both males and females, are entirely asymptomatic (13). Therefore, the need for *Ureaplasma* and *Mycoplasma* screening in sexually active individuals should be emphasized, considering the potential serious outcomes despite clinical silence.

Mycoplasma hominis, a member of the Mycoplasmataceae family within the Mollicutes class, typically resides as a commensal in the lower urogenital tract of healthy individuals. However, under specific conditions, *Mycoplasma hominis* can lead to various genital infections, such as bacterial vaginosis, pelvic inflammatory disease and cervicitis. This microorganism has been associated with pregnancy complications and neonatal diseases (14). In men, *Mycoplasma hominis* can cause urethritis and prostatitis, while studies have indicated its potential pathogenic role in infertility in both men and women (1,3). Interestingly, *Mycoplasma hominis* has also been linked to a range of extragenital infections, including septic arthritis, endocarditis and brain abscesses, particularly in immunocompromised patients (14).

Mycoplasma genitalium, first isolated from urethral swabs of symptomatic men with non-gonococcal urethritis, has been associated with various urethral diseases. While its strong association with non-gonococcal urethritis is well established, the impact of *Mycoplasma genitalium* on male fertility remains uncertain (15). Emerging data suggest a

connection between chronic asymptomatic genital infection with *Mycoplasma genitalium* and fallopian tube disorders, pelvic inflammatory disease, infertility and preterm birth, but the exact risk for female genital tract infections is yet to be determined (16). Research concerning the role of Ureaplasmas and Mycoplasmas in male infertility is increasing, but the involvement of *Mycoplasma genitalium* and *Ureaplasma parvum* remains underexplored. The role of *Ureaplasma urealyticum* and *Mycoplasma hominis* in male infertility is controversial (17). While these microorganisms can colonize the male reproductive tract, their contribution to male infertility is still debated. The existing studies have not found a clear association between altered semen parameters and the presence of these bacteria in semen (1,18).

A meta-analysis comparing positive samples between infertile and fertile men found a connection between the risk of infertility and the presence of *Ureaplasma urealyticum* and *Mycoplasma hominis*. By contrast, no association was found with *Ureaplasma parvum* and *Mycoplasma genitalium*. Nevertheless, the observation of *Mycoplasma genitalium* attaching to spermatozoa and the microorganism being able to be carried by motile sperm suggest a potential role in infertility. A significant difference in the detection rates was observed for *Ureaplasma urealyticum* (10.22 vs. 3.65%) and *Mycoplasma hominis* (3.16 vs. 0.89%) between infertile subjects and controls. Furthermore, a major difference in progressive motility, total motility and typical forms was demonstrated when comparing the infertile group with or without *Ureaplasma urealyticum* infection. The presence of *Ureaplasma urealyticum* was linked with a significantly higher production of semen ROS and malondialdehyde. Oxidative stress induced by *Ureaplasma urealyticum* can cause DNA damage and affect male fertility. Male fertility can be negatively impacted by *Ureaplasma urealyticum* due to various pathophysiological mechanisms. The expression of P34H, which is a protein essential for sperm and zona pellucida interaction, is reduced in the presence of *Ureaplasma urealyticum*. Furthermore, the activity of hyaluronidase, an enzyme essential for the acrosome reaction, is also lowered. This results in increased DNA fragmentation. These findings help us understand how bacterial infections can interfere with subtle mechanisms that are not typically examined during male infertility investigations, and thus potentially impair reproduction (1,3,19,20).

There are limited data regarding the impact of Mycoplasmas and Ureaplasmas on the success rates of assisted reproductive technologies, such as *in vitro* fertilization (IVF). Early studies suggest that *Ureaplasma* infections may reduce pregnancy rates during IVF, with a higher risk of miscarriage in infected individuals. One study indicated that the infected group had a higher risk of miscarriage, potentially associated with maternal infection (1). These findings highlight the need for further research in order to understand the effects of these microorganisms on IVF outcomes (21,22).

3. Association between infertility caused by Mollicutes and resistance to antibiotics

Importance of antibiotic resistance. Urogenital infections are documented as significant factors contributing to infertility, a condition that affects 15-20% of reproductive-aged couples globally, with both men and women being equally accountable in cases of infertility (5). By implementing education, screening and appropriate treatment for individuals testing positive for infections, it is possible to effectively reduce the risks of infections and infertility.

Many urogenital infections are asymptomatic and can become chronic, causing numerous serious complications, most importantly infertility. Hence, they should be screened for in any sexually active patient. It is well known that genital infection with either one of the Mollicutes can cause infertility problems in both male and female patients. Therefore, it is crucial to avoid empirical treatment and the treatment of partners without evidence, as these practices contribute to bacterial resistance and consequently elevate the incidence of genital complications.

Prevalence rates in men and women. The prevalence of *Mycoplasma hominis* and *Ureaplasma urealyticum* has been increasing in females experiencing infertility (13). Studies have reported that *Mycoplasma hominis* and *Ureaplasma urealyticum* are present in an estimated 2.0-40.5% of females with infertility globally, with prevalence rates among asymptomatic females ranging from 7-16% (13,23). Conversely, a meta-analysis from China indicated that *Ureaplasma parvum* positivity in infertile men displayed no association with male infertility, while *Ureaplasma urealyticum* positivity was significantly associated with male infertility. Similar results were obtained for *Mycoplasma hominis* compared to *Mycoplasma genitalium*; as for the latter, there was no association with male infertility (17). However, previous studies have primarily focused on the role of *Ureaplasma* in male and female infertility without distinguishing between *Ureaplasma urealyticum* and *Ureaplasma parvum* (1).

Existing data demonstrated that infections with *Mycoplasma hominis* are more prevalent in males than females (20.6 compared to 5.7%), yet genital infections with *Mycoplasma genitalium* affect more females than males (8.6 and 7.4%, respectively) (24). An Argentinean study concluded that *Ureaplasma* and *Mycoplasma hominis* infections were more commonly associated with female patients, as male patients were at a lower risk of Mollicutes infection than females (5). Conferring to the existing data, *Ureaplasma* is detected in nearly 25% of patients with genital tract infections, with a majority being females; in ~21% of the cases, they are infertile women. *Mycoplasma hominis* is detected in 12% of patients with similar clinical scenarios to those stated above. Coinfection with *Ureaplasma* and *Mycoplasma hominis* is detected less frequently in patients with genital tract infection and infertility (25). Data from the literature suggest that different types of Mollicutes can have distinctive implications for female patients. *Mycoplasma genitalium* was reported to be an important risk factor for female infertility and preterm birth, but not for spontaneous abortion, while *Ureaplasma urealyticum* had no significant effect on female infertility. However, coinfection with *Mycoplasma hominis* and *Ureaplasma* was associated with female infertility, spontaneous abortion and stillbirth (26).

Furthermore, *Ureaplasma parvum* is more prevalent than *Ureaplasma urealyticum*, with serovar 3/14 being the

most frequently detected serovar. While the difference in detection rates of different serovars of *Ureaplasma parvum* was not statistically significant, the predominance of serovar 3/14 suggests a potential pathogenic role (25,27). However, a detailed study revealed that *Ureaplasma parvum* serovars 1 and 6, along with *Ureaplasma urealyticum* serovar 9, are the most common serovars identified in the urogenital tract of infertile males. The combination of variable serovar-specific genes of *Ureaplasma* with known virulence factors may influence the development of pathological processes on the mucosal surface of the human genital tract, highlighting the need for further research to confirm serovar distribution and their potential pathogenic roles in different clinical settings (28).

Mycoplasma hominis and *Ureaplasma* are implicated in a wide range of infections that can lead to infertility. Chronic genital infections in females may result in adhesions within and around the fallopian tubes, leading to tube obstruction and hindering the union of sperm and egg. These infections are also linked to ectopic pregnancies and premature rupture of membranes, reducing the chances of conception (2,29). Mollicutes, including *Mycoplasma hominis* and *Ureaplasma*, are specifically associated with sperm abnormalities, such as abnormal motility, impaired mitochondrial function and DNA integrity loss (2,30). The presence of *Mycoplasma hominis* in the genital tract is significant, as it contributes to a polybacterial infection known as 'bacterial vaginosis'. This condition, characterized by dysbiosis due to the absence of Lactobacilli and an increase in vaginal pH, promotes further infections. Studies in the Italian population have reported a higher prevalence of *Ureaplasma urealyticum* and *Mycoplasma hominis*, with a potential association of *Mycoplasma hominis* with bacterial vaginosis (2,31,32).

A group of Austrian physicians conducted a study suggesting a potential protective effect of probiotic supplements on the vaginal microbiota. The study indicated that probiotics help contain the growth of harmful bacteria, including *Ureaplasma parvum*, potentially offering insight into the interaction between *Lactobacillus* species and *Ureaplasma parvum*. Further research is needed to explore the use of probiotics in gynecological disorders, potentially leading to innovative approaches in infertility therapy (33).

Importance of genetics and studies related to the genetic debate. An American study analyzing the genomes of *Ureaplasma urealyticum* and *Ureaplasma parvum* revealed that the classification of *Ureaplasma* isolates into distinct serovars was primarily based on differences in the major surface antigen. Whole-genome analysis indicated that the two species and 14 serovars are highly similar at the genome level. *Ureaplasma urealyticum* was found to be more capable of acquiring genes horizontally, potentially contributing to its increased virulence in certain conditions. The study suggested that Ureaplasmas exist as quasi-species rather than stable serovars in their natural environment, with differential pathogenicity likely influenced by factors beyond serovar differences, such as the presence of pathogenicity factors in individual clinical isolates and variations in autoimmunity and microbiome among patients. Novel mechanisms of antibiotic resistance in bacteria may induce microbiota dysbiosis, facilitating bacterial migration and translocation, potentially causing more significant damage to reproductive organs (9,34,35).

A group of researchers from Tunisia conducted an analysis of genetic diversity and phylogenetic relationships among 59 clinical isolates of *Mycoplasma hominis* from Tunisia, classified as pathotypes associated with gynecological infections or infertility. They developed an expanded multilocus sequence typing (eMLST) scheme by combining previously reported MLST loci with a new set of putative virulence genes known as multi-virulence-locus sequence typing loci. This approach led to the segregation of the *Mycoplasma hominis* population into two distinct genetic lineages, each linked to a specific pathotype. The study revealed evidence of recombination, although not significant enough to disrupt the overall clonal population structure of *Mycoplasma hominis*, likely due to purifying selection favoring the most adapted clones. The eMLST scheme provided valuable insight into the phylogenetics of *Mycoplasma hominis*, suggesting the presence of genetically distinct urogenital pathotypes. The data indicated that *Mycoplasma hominis* undergoes genetic diversification through a combination of mutation and recombination while maintaining its pathotype distribution throughout its purifying selection. These findings highlight the need for further validation studies using larger, geographically diverse and well-defined clinical strain collections to thoroughly investigate the genetic relationships among different *Mycoplasma hominis* pathotypes and their implications in human infertility. Additionally, there are studies in the literature that emphasized the existence of specific epidemic clonal lineages of *Ureaplasma urealyticum* that are more likely to be transmitted between partners in infertile couples and associated with clinical symptoms (36-39).

Another intriguing study revealed that following *Ureaplasma* infection in the male reproductive tract, the balance of seminal plasma components can be significantly disrupted, making sperm quality highly susceptible to various factors in seminal plasma. Human polymorphonuclear elastase (PMN elastase) was identified as a common spermatic elastase, influencing sperm concentration and motility. Changes in PMN elastase concentration were linked to inflammatory responses that could affect sperm parameters and male fertility. In addition, the study observed significant changes in semen characteristics before and after treatment, highlighting the impact of reproductive tract infections on semen quality. Furthermore, the research suggested that inflammation resulting from genital tract infections could alter the pH and physical properties of semen, affecting sperm parameters and fertility. The presence of Mollicutes, such as *Ureaplasma*, in seminal plasma could influence sperm characteristics and promote the production of certain substances, potentially leading to adverse effects on male reproductive health. The study underlined the importance of understanding the complex interactions between pathogens and seminal plasma components in the context of male fertility (40-46).

Diagnostic methods. The laboratory diagnosis of genital Mollicutes plays a crucial role in preventing infertility. While the culture approach for detecting bacterial infections has demonstrated good sensitivity and specificity, nucleic acid amplification tests offer significantly higher sensitivity,

particularly for asymptomatic infections with low bacterial loads, presenting a notable advantage. Multiplex PCR assays can detect up to eighteen different organisms, providing a valuable option for patients with pathogen coinfections. These technologies exhibit comparable sensitivity and specificity to their respective singleplex assays, addressing the challenge of distinguishing between *Ureaplasma urealyticum* and *Ureaplasma parvum*, which cannot be differentiated in culture (3). A crucial matter to address is that different countries use various laboratory techniques and this may cause confusion in differentiating between *Ureaplasma urealyticum/parvum* and *Mycoplasma hominis/genitalium*. For example, one of our laboratories does not always provide a distinction between *Ureaplasma parvum* and *urealyticum*. For those reasons, when the testing comes back positive for *Ureaplasma* '*parvum*', it is treated accordingly. The same principle applies to *Mycoplasma*. Furthermore, we always advise screening for Mollicute infection in sexually active adults and, if present, perform an antibiogram, since they are naturally resistant to penicillin. In addition, over the years, the Mollicutes have been developing resistance to more classes of antibiotics because of the unnecessary widespread use of antibiotics. Therefore, treatment guidelines should be followed (6).

Mechanisms of drug resistance and effective treatments. Although Mollicutes evolved from Gram-positive ancestors, they lack a cell wall and are typically treated with quinolones, tetracyclines or erythromycin. However, the prevalence of resistant strains of *Mycoplasma hominis* and *Ureaplasma urealyticum* is increasing annually due to the widespread use of these antibiotics (47). According to literature, the ciprofloxacin resistance of *Ureaplasma urealyticum* isolates was very high (52%), with lower resistance rates observed for other tested antibiotics (ofloxacin, 16%; erythromycin, 16%; clarithromycin, 10%; azithromycin, 8%; tetracycline, 6%; pristinamycin, 3%; josamycin, 2%; and doxycycline, 2%). For *Mycoplasma hominis*, the highest resistance rates were recorded for ciprofloxacin (80%) and macrolides (azithromycin, 40%; clarithromycin and erythromycin, 30% each), followed by ofloxacin (30%). Lower resistance rates were registered for tetracycline (16%), josamycin (11%), pristinamycin (11%) and doxycycline (11%) (6,47). Of note, doxycycline remains highly effective against both *Mycoplasma hominis* and *Ureaplasma urealyticum* (6,25,48-51). Various mutations have led to antibiotic resistance in Mollicutes, with specific mutations identified in levofloxacin-resistant *Ureaplasma* strains (ParC S83L and ParE R448K) and quinolone-resistant *Mycoplasma hominis* (GyrA S153L and ParC S91I) (6,52). Mutations in the 23S rRNA gene account for intrinsic resistance to macrolides in *Mycoplasma hominis* (53). Macrolide resistance is an urgent health problem, with resistance rates currently estimated at 30-100% for *Mycoplasma genitalium* (54). Resistance to tetracycline is attributed to the tet(M) mutation observed in both *Ureaplasma* and *Mycoplasma hominis* strains worldwide (55-57). Despite reported resistance to certain antibiotics, doxycycline consistently demonstrates efficacy against both pathogens (6,25,58,59). Studies have shown varying incidences of antibiotic resistance genes among Mollicutes populations, influenced by factors such as geographical location, population demographics and study methodologies. The diversity in results underscores the complexity of characterizing antibiotic resistance in Mollicutes and the importance of tailored treatment approaches based on regional resistance patterns and individual patient factors (5,13). The prevalence of Mollicutes infections represents a contemporary healthcare challenge due to intrinsic mutations and the reliance on empirical treatment modalities for such infections. Furthermore, enhanced classification and comprehension of commensal and opportunistic pathogens are imperative, given the present data suggesting caution against empirical treatment of genital infections (60). We advocate for conducting antibiogram assessments to ascertain pathogen resistance profiles, prompting a shift from fluoroquinolones to macrolides to tetracycline-based therapies.

At present, scientists are engaged in the exploration of antigenic proteins responsible for triggering the immune response, facilitating a rapid immune reaction upon reinfection. A recent innovative investigation introduced a peptide-based vaccine targeting *Ureaplasma urealyticum*, employing molecular docking and molecular dynamics simulation techniques. This study identified new potential vaccine candidate proteins that exhibit antigenic properties, are membrane-bound and are non-allergenic. The findings of the present study suggested that the identified vaccine candidate proteins have the potential to elicit robust and long-lasting protective immunity against *Ureaplasma urealyticum* in forthcoming applications (8,61).

In the authors' opinion, the increasing availability of data on the genome of Mollicutes and their mechanism of action is critically important for advancing clinical practices. This increasing amount of knowledge offers valuable insight into the pathogenic processes of Mollicutes, which can significantly enhance clinicians' ability to effectively manage and treat patients facing infertility. As research continues to unveil the genetic intricates and biological behaviors of these microorganisms, healthcare providers will be better equipped to develop targeted therapies and preventive strategies, ultimately improving patient outcomes in reproductive health.

The limitation of this paper is represented by the inclusion of different studies from around the world with different laboratory techniques, which may cause confusion in differentiating between *Ureaplasma urealyticum/parvum* and *Mycoplasma hominis/genitalium*. It is a well-known fact that all these pathogens may cause genital infections challenging individuals in the reproductive area. However, differences between males and females can affect the overall outcome. Latest studies indicate that screening for and treating *Ureaplasma parvum* is unnecessary, as it has been shown to be merely a commensal organism (62). However, due to faulty detection methods, certain laboratories group *Ureaplamsa urealyticum* and *Ureaplasma parvum* under one name. Therefore, improved detection techniques are essential. In subsequent research attempts, it is essential for scientists to direct their efforts towards scrutinizing particular genes within the genome of each strain of Mollicutes, in order to enhance the precision and efficacy of antibiotic therapies, therefore reducing the resistance rates.

4. Conclusions

The identification of Mollicutes infection in infertile couples is not currently part of the standard infertility testing protocols,

primarily due to limited evidence linking Mollicutes to infertility and a lack of awareness among healthcare providers regarding infertility caused by Mollicutes infections. Despite being asymptomatic, these infections should be screened for, as they can lead to various serious complications, particularly infertility in both male and female patients. It is essential to promote the understanding among clinicians regarding the appropriate use of antibiotics in order to prevent treatment failures and the development of antibiotic-resistant strains. In the future, a comprehensive prospective case-control study that considers different strains of *Ureaplasma* and *Mycoplasma*, the presence of other microorganisms, the level of PMN elastases as an inflammation marker and the number of sexual partners will be critical for confirming or disproving the role of Mollicutes in infertility. Increasing awareness of the importance of screening for Mollicutes infections and conducting further research will be essential for addressing infertility issues associated with these infections.

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Authors' contributions

AC performed the critical review of literature findings and wrote the paper. DB conceived and designed the study. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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