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Evaluation and Management of Male Genital Tract Infections in the Setting of Male Infertility: An Updated Review

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Abstract

PURPOSE OF REVIEW: Male infertility may be secondary to male genital tract infection (MGTI) in an estimated 15% of cases. In the absence of overt clinical signs, evaluation for MGTI beyond semen analysis is not well established. Therefore, we review the literature on the evaluation and management of MGTI in the setting of male infertility.

RECENT FINDINGS: A set of international guidelines recommends semen culture and polymerase chain reaction testing, but the significance of positive results remains unclear. Clinical trials evaluating anti-inflammatory or antibiotic treatment report improvements in sperm parameters and leukocytospermia, but data on the effect on conception rates are lacking. Human papillomavirus (HPV) and the novel coronavirus (SARS-CoV-2) have been associated with poor semen parameters and decreased conception rates.

SUMMARY: The finding of leukocytospermia on semen analysis prompts further evaluation for MGTI including focused physical examination. The role of routine semen culture is controversial. Treatment options include anti-inflammatories; frequent ejaculation; and antibiotics, which should not be used in the absence of symptoms or microbiological infection. SARS-CoV-2 represents a subacute threat to fertility that should be screened for in the reproductive history along with HPV and other viruses.

Keywords

male; infertility; genital; infection

INTRODUCTION

Infertility, defined as inability to achieve pregnancy within 1 year of regular and unprotected sexual intercourse, is estimated to affect 8–30% of reproductive-aged couples worldwide

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Conflicts of interest

None.

[1–3]. Male factor infertility alone accounts for 20–30% of cases but contributes to 50% of cases overall.[4] It is attributable to male genital tract infection (MGTI) in 15% of cases [5–7], making MGTI the third most common cause of male factor infertility after idiopathic infertility (28.4%) and varicocele (18.1%) [8]. Despite this prevalence, there is a lack of consensus among male reproductive specialists regarding how and when to investigate infectious etiologies in the absence of overt clinical symptoms. Here, we review the evaluation and management of MGTI in the setting of male infertility.

INITIAL EVALUATION

The initial evaluation of male infertility consists of a comprehensive history and physical examination followed by semen analysis. Men presenting for fertility evaluation rarely have overt clinical symptoms (e.g., dysuria, pelvic pain, scrotal pain) suggesting presence of MGTI [9]. Therefore, the concern for infection as the cause of male infertility typically begins with the finding of round cells on semen analysis (SA). The American Urological Association (AUA) states that increased round cells on SA, defined as $>1 \times 10^6$ round cells/mL, should be further evaluated to differentiate white blood cells (WBCs) from native cells of the urogenital tract [10**]. WBCs are a marker of inflammation and may be secondary to infection. Alternatively, round cells may represent germ cells, epithelial cells, and/or degenerated spermatozoa, which are not directly associated with inflammation or infection [11*,12].

The differentiation of round cells may be performed with peroxidase staining [13], Papanicolaou staining [14,15], flow cytometry [16,17], or leukocyte antigen (e.g., CD45) immunohistochemistry [18,19*]. Both the AUA and the American Society for Reproductive Medicine (ASRM) recommend immunohistochemistry as the gold standard for identifying seminal leukocytes given the high sensitivity and specificity of this technique [20]. However, immunohistochemistry is relatively expensive and time-consuming. The World Health Organization (WHO) thus recommends peroxidase staining as an initial test, with follow-up flow cytometry or immunohistochemistry if the resources are available and further differentiation is needed [19*].

The finding of $>1 \times 10^6$ WBCs/mL is defined as leukocytospermia [20], which may represent a threat to fertility since WBCs generate reactive oxygen species that damage sperm [21,22]. Leukocytospermia is found in 10–20% of infertile men [23]. Elevated seminal leukocytes are associated with abnormal sperm morphology, increased DNA fragmentation index, and significant reductions in sperm concentration and sperm motility [24–26]. Although elevated seminal leukocytes are not statistically correlated with bacteriospermia [26], the association between WBCs and inflammation has led to WHO acknowledging in their manual for human semen analysis that leukocytospermia may be associated with infection and poor sperm quality [19*]. However, there is no direct association between seminal leukocyte concentration and conception rate [27], which is reflected in the AUA's assertion that seminal leukocyte concentration is not a test of fertility [10**].

Many non-infectious causes of leukocytospermia, such as environmental toxins, substance use, varicocele, autoimmune disorders, and nonbacterial chronic prostatitis have been proposed [26]. If non-infectious etiologies are absent, patients with confirmed leukocytospermia should be evaluated for underlying infection [10**]. A major issue is that there is a lack of formal guidelines specifying the components of this evaluation [20]. For starters, the provider may consider a repeat physical examination, employing focused techniques such as stripping the urethra, palpation of the epididymis, and digital rectal exam to evaluate for urethritis, epididymitis and prostatitis, respectively. Positive exam findings would indicate confirmatory laboratory tests (e.g., urinalysis, urine culture) and appropriate antibiotic treatment [28].

SEMEN MICROBIOLOGICAL ANALYSIS

If there are no positive physical examination findings, the clinician may consider further testing of the semen. While the AUA does not specify such tests, the European Association of Urology (EAU) states that leukocytospermia should be further investigated with semen culture or polymerase chain reaction (PCR) for common genital tract pathogens [29**]. Peroxidase staining with reflexive semen culture may be more cost-effective compared to peroxidase staining alone, given the potential health and cost expenses associated with infection transmission during assisted reproductive technology (ART) procedures [30].

Incidence of positive semen cultures ranges from 6% to 68% based on contemporary studies [31–33*]. This is likely due to differences in laboratory methods (e.g., incubation time, incubation temperature, culture media) and possible contamination by urethral, meatal, and skin flora. The organisms most commonly found on semen culture are gram-positive cocci, including *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp.; and Enterobacteriaceae, including *Escherichia coli* [28,31,34,35]. It should be noted that the common genital tract pathogens *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Neisseria gonorrhoeae* have fastidious growth requirements and are best identified with semen PCR [28,31,36]. Thus, combined microbiological analysis with semen culture and PCR detects a wider range of organisms than either technique alone. A summary of pathogenic male genital tract bacteria and their associated syndromes, diagnostic tests, and treatments is provided in Table 1.

However, data supporting the clinical utility of semen cultures are lacking. A study using both semen culture and PCR demonstrated that there are no significant differences in the prevalence of *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis* between infertile and fertile men, though the presence of *Ureaplasma urealyticum* was associated with lower mean sperm concentration and lower sperm vitality [37]. Despite only three organisms being investigated, this finding suggests that there are minimal differences in microbiology between fertile and infertile men. In another study, semen cultures performed for men attending an infertility clinic (n = 85) revealed that asymptomatic bacteriospermia did not correlate with abnormal semen parameters [34].

Eini et al. performed semen cultures for men presenting to an infertility clinic (n = 172) and found that leukocytospermia and sperm DNA fragmentation were significantly

higher in men with infected samples, relative to those with uninfected samples. There was also deterioration in sperm concentration and motility of infected samples [35].[35] Ricci et al. performed a microbiological analysis, including both culture and PCR, of both vaginal/endocervical swabs and semen samples from infertile couples [36].[36] This revealed that seminal *Enterococcus faecalis* was associated with deterioration in sperm motility and morphology. Additionally, *Enterococcus faecalis*, *Ureaplasma urealyticum*, and/or *Mycoplasma hominis*, when found in either partner's sample, was associated with failed in vitro fertilization [36].[36] A systematic review of semen microbiological studies published between 1992 and 2019 found an increased prevalence of *Ureaplasma urealyticum* in infertile men [33*].[33] In addition, *Enterococcus faecalis*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis* have been associated with deterioration of semen parameters [33*,38,39].[33,38,39]

Overall, the clinical relevance of semen culture remains controversial. There is a dearth of literature associating the semen microbiome with natural conception outcomes, and it remains to be seen whether semen culture-guided antibiotics are superior to empiric antibiotics.

TREATMENT

In the absence of consensus guidelines, there have been multiple algorithms proposed for the treatment of male infertility with leukocytospermia and concern for MGTI [11*,28,40].[11,28,40] Localizing infectious symptoms (e.g., dysuria, pelvic pain, scrotal pain) or positive physical exam findings (e.g., urethral discharge, prostatic tenderness, epididymal tenderness) may indicate an infectious syndrome such as urethritis, prostatitis, or epididymitis, each of which has its own established treatment guidelines [28]. However, as previously mentioned, MGTIs are often clinically asymptomatic in the context of male infertility workup [9].

Anti-inflammatories

In the setting of male infertility with leukocytospermia and absence of infectious symptoms, the algorithm proposed by Velez et al. eschews semen microbiological analysis, recommending direct treatment with an anti-inflammatory such as ketotifen, valdecoxib, or rofecoxib [11*]. Insofar as leukocytospermia represents inflammation of the male genital tract, the aforementioned medications may be useful because they target non-specific inflammatory processes regardless of whether an infection is present. Use of anti-inflammatories is backed by clinical trials in which treatment resulted in significant improvement of sperm parameters and reduction of seminal leukocytes [41–43]. In the trial evaluating rofecoxib, a 15.8% natural pregnancy rate was achieved after treatment, although no control group was available for comparison [43]. These trials are limited by small sample size and lack of follow-up studies. Nonetheless, given their demonstrated efficacy and lack of adverse effects, anti-inflammatories represent a reasonable treatment option for leukocytospermia when an infectious organism has not been identified (Figure 1).

Antibiotics

In the aforementioned algorithm, anti-inflammatory treatment is followed by repeat semen analysis with peroxidase staining (or other WBC differentiation technique). If leukocytospermia is persistent, antibiotic therapy—doxycycline or trimethoprim-sulfamethoxazole—may be considered [11*]. Antibiotic therapy for male infertility with concern for asymptomatic MGTI is controversial. Many of the clinical trials evaluating such treatments (e.g., doxycycline, TMP-SMX) are from the twentieth century and found no improvement in sperm parameters [44–47]. Though, two of these trials demonstrated reduction of leukocytospermia, with an enhanced effect observed when antibiotic treatment was accompanied by frequent ejaculation [45,46]. A subsequent meta-analysis concluded that antibiotic treatment of male infertility results in increased semen volume, sperm concentration, sperm motility, and normal-form sperm [48]. A more recent clinical trial evaluating antibiotic treatment of asymptomatic MGTI caused by CT or UU also demonstrated significant improvement in all sperm parameters [49], but there remains insufficient evidence that antibiotic treatment increases the rate of conception [44–46,49,50]. Thus, in the absence of clinical infectious symptoms or an isolated pathogen, antibiotic treatment is generally not recommended, but can be attempted if leukocytospermia is refractory to anti-inflammatory treatment (Figure 1).

VIRUSES

The strategies discussed above recognize bacteria as pathogens. Viruses represent another major concern, especially in light of the recent global coronavirus disease 2019 (COVID-19) pandemic, which has been found to affect the male genital tract [51,52]. There are multiple genital tract viruses associated with male infertility including mumps virus, human immunodeficiency virus, hepatitis B and C viruses, and zika virus [53,54]. In the remaining sections, we review human papillomavirus (HPV) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to their current prevalence and recent evidence of impact on male fertility.

HPV

HPV is the most common virus of the reproductive tract and the most commonly sexually transmitted infection in the United States. More than 200 types have been identified [55]. Low-risk HPV strains cause oral and anogenital warts, while high-risk strains such cause cervical cancer in women and oropharyngeal, anal, and penile cancer in men [56,57]. However, most HPV infections are asymptomatic [57,58].

With regards to male infertility, HPV-positive semen has been significantly associated with deterioration in sperm count, sperm motility, sperm morphology, and DNA fragmentation index compared to HPV-negative semen [59–61,62*,63–65]. HPV-positive semen has also been associated with decreased pregnancy rate and increased miscarriage rate in couples undergoing assisted reproductive technology (ART) procedures such as in vitro fertilization and intrauterine insemination [61,66,67].

The clear association of HPV-infected semen with poor semen parameters and poor ART outcomes calls for effective prevention and management of HPV infection in infertile couples. One strategy is sexual hygiene counseling (e.g., hygiene of the reproductive tract, avoiding oral and anal sex), which has been shown to significantly reduce HPV persistence in infected couples [68]. Another strategy is post-exposure HPV vaccination; in a retrospective study, administering the vaccine to men with HPV detected in semen who were in infertile relationships resulted in significantly increased pregnancy rates and decreased miscarriage rates compared to non-vaccinated HPV-positive men. The vaccinated men were also shown to have increased sperm motility and decreased anti-sperm antibody levels [69]. More data is needed before altering management guidelines for HPV-infected patients undergoing ART procedures.

SARS-CoV-2

In addition to causing the respiratory disease COVID-19, SARS-CoV-2 has been found to affect the male reproductive system. Since SARS-CoV-2 infects cells by binding the angiotensin-converting enzyme 2 (ACE2) receptor [70], cells that are high in ACE2 expression, such as testicular spermatogonia, Leydig cells, and Sertoli cells, are highly susceptible to SARS-CoV-2 [71,72].

In semen samples collected from patients 30 days after testing positive for SARS-CoV-2, the sperm concentration was significantly reduced compared to an age-matched, uninfected control group [73]. In a Belgian cohort study, sperm concentration and progressive motility were signific8antly reduced relative to baseline within the first month after COVID-19 infection, with gradual improvement of sperm parameters over 6 months [74*]. Additionally, male SARS-CoV2 infection was found to have a mildly negative impact on fecundability, but with increased fecundability observed sixty days after infection [75]. These findings suggest that COVID-19 has a negative but short-lived impact of male infertility, with improvement in sperm parameters and conception rate multiple months after infection.

While there are currently no treatments for COVID-19-related infertility, vaccines have become widely available for the prevention of COVID-19. In a recent cohort analyzing the impact of the Pfizer-BioNTech vaccine on sperm parameters, patients who received two doses of the vaccine did not experience any change in semen parameters from before to 14 months after vaccination [76*]. This finding has been supported by recent meta-analyses [77,78], indicating that COVID-19 vaccines do not affect male fertility. More data on the effect of male COVID-19 infection on conception rates are needed to inform further management guidelines.

CONCLUSION

MGTI is a major cause of male infertility that should be accounted for in the reproductive history and physical examination. In the absence of clinical signs or symptoms, the concern for MGTI begins with the finding of leukocytospermia, which may be further investigated with semen culture and PCR based on the clinician’s discretion. However, further research is needed to verify the utility of semen microbiological analysis. Treatment for MGTI in the setting of male infertility includes anti-inflammatory agents or antibiotics, the former

being preferred if no pathogenic organism has been detected. Finally, the physician should be aware of not only bacteria, but also common viruses such as HPV and SARS-CoV-2 as causes of MGTI and associated infertility.

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KEY POINTS

- The finding of leukocytospermia on semen analysis can be further evaluated with semen culture and polymerase chain reaction, but the clinical relevance of positive results is not fully established.
- Leukocytospermia can be treated with anti-inflammatory agents, though antibiotics are preferred if there is clinical or microbiological evidence of infection
- In addition to bacteria, common viruses such as human papillomavirus (HPV) and the novel coronavirus (SARS-CoV-2) can infect the male genital tract and cause infertility.

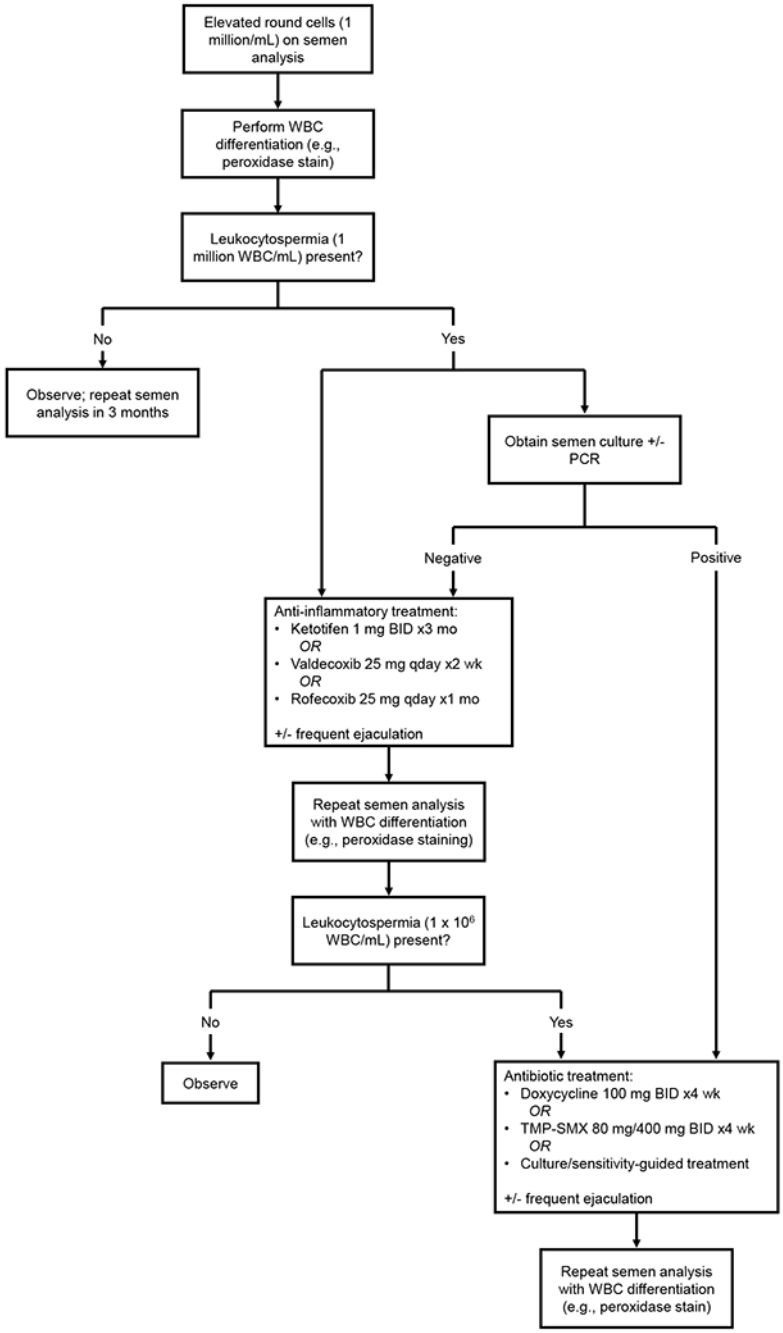

Figure 1.

Diagnosis and treatment of leukocytospermia in the setting of male infertility

WBC: white blood cell(s), PCR: polymerase chain reaction, BID: twice a day, qday: every day, TMP-SMX: trimethoprim-sulfamethoxazole.

Table 1.

Pathogenic bacteria of the male genital tract

Organism	Associated clinical syndromes	Diagnostic test of choice	Antibiotic treatment
Chlamydia trachomatis	Urethritis Prostatitis Epididymitis	NAAT (e.g., PCR)	Doxycycline 100 mg PO BID x 7 days
Ureaplasma urealyticum	Urethritis	NAAT (e.g., PCR)	Doxycycline 100 mg PO BID x 7 days
Mycoplasma hominis	-	NAAT (e.g., PCR)	Doxycycline 100 mg PO BID x 7 days
Neisseria gonorrhoeae	Urethritis Epididymitis	NAAT (e.g., PCR)	Ceftriaxone 500-1000 mg IM once
Enterobacteriaceae (e.g., *Escherichia coli*)	Prostatitis Epididymitis	Culture	Levofloxacin 500 mg PO qday x 10 days *OR* TMP-SMX 160mg/800mg PO BID x 10 days
Gram-positive cocci (e.g., *Enterococcus* spp.)	Prostatitis	Culture	Amoxicillin 500 mg PO TID x 5 days *OR* Nitrofurantoin 100 mg PO BID x 5 days *OR* Fosfomycin 3 g PO once

NAAT: nucleic acid amplification test, PCR: polymerase chain reaction, spp.: species, PO: per os, qday: every day, BID: twice a day, IM: intramuscular.