

Semen culture and the assessment of genitourinary tract infections

Michael Solomon, Ralf Henkel*

Department of Medical Biosciences, University of the Western Cape, Bellville, South Africa

*E-mail: rhenkel@uwc.ac.za

ABSTRACT

The male factor contributes approximately 50% to infertility-related cases in couples with an estimated 12%–35% of these cases attributable to male genital tract infections. Depending on the nature of the infection, testicular sperm production, sperm transport, and sperm function can be compromised. Yet, infections are potentially treatable causes of infertility. Male genital tract infections are increasingly difficult to detect. Moreover, they often remain asymptomatic (“silent”) with the result that they are then passed on to the relevant sexual partner leading to fertilization and pregnancy failure as well as illness of the offspring. With the worldwide increasing problem of antibiotic resistance of pathogens, proper diagnosis and therapy of the patient is important. This testing, however, should include not only aerobic microbes but also anaerobic as these can be found in almost all ejaculates with about 71% being potentially pathogenic. Therefore, in cases of any indication of a male genital tract infection, a semen culture should be carried out, particularly in patients with questionable semen quality. Globally, an estimate of 340 million new infections with sexually transmitted pathogens is recorded annually. Among these, the most prevalent pathogens including *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, and *Mycoplasma hominis*. *Escherichia coli* are considered the most common nonsexually transmitted urogenital tract microbes. These pathogens cause epididymitis, epididymo-orchitis, or prostatitis and contribute to increased seminal leukocyte concentrations.

INTRODUCTION

In the assessment of a genitourinary tract infection, semen culture is considered an important diagnostic tool as genitourinary tract infections and inflammations are potential causes for male infertility. Semen is comprised of spermatozoa and secretions from the accessory sex organs.^[1] The glands and organs that contribute to the semen are considered sterile. The sterility of the internal urethra is maintained by the normal flow of urine; however, the distal urethra is not considered a sterile area. Therefore, the culturing of semen samples usually yields growth of organisms, many of which are considered to be normal flora of the genitourinary tract.^[2]

Studies have suggested that genitourinary tract infections account for up to 15% of cases of male

infertility.^[3] Semen contamination arises from the urinary tract of patients or can be sexually transmitted from the partner by pathogens such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. The presence of other pathogens in concentrations greater than 10^3 bacteria/ml ejaculate (bacteriospermia) is clinically regarded as a sign of an active infection.^[4] Differentiating active infections of the genitourinary tract from commensal microflora is difficult. Infections, acute or chronic, may compromise spermatogenesis and sperm function. The type and severity of an infection can be identified by a positive semen culture by quantifying the colony forming units and determination of antibiotic susceptibility. The terms bacteriospermia and infection are to be distinguished from inflammation since the latter is the response of tissues to an infection. Among infertile men, studies report a prevalence of infections between 11.6% and 45% in

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cases with a history of urethral discharge as an marker of infection.^[5,6]

Male genital tract infections are difficult to detect as they are asymptomatic in many cases and often remain undiagnosed unless the patient seeks treatment for specific symptoms.^[7] Yet, in light of the increasing number of patients seeking treatment for impaired fertility using assisted reproduction (intrauterine insemination, *in vitro* fertilization, or intracytoplasmic sperm injection), the diagnosis of “silent” genital tract infections should receive attention as the infection may be linked to asthenozoospermia.^[8] Infections are potentially treatable causes of male infertility and resistance to common antibiotics and poor compliance may impede the efficacy of antibiotics in resolving complicated UTI or restoring fertility.^[9-11]

FACTORS INFLUENCING THE FERTILITY POTENTIAL OF SPERMATOZOA

In asymptomatic patients, leukocytes frequently appear in ejaculates, even in those from fertile men.^[12] Numerous studies have shown that leukocytes are powerful producers of reactive oxygen species (ROS) and may have detrimental effects on sperm function and sperm DNA integrity.^[13,14] Despite the WHO^[4] recognizing that the presence of leukocytes is indicative of an infection, several studies^[15,16] found that the detection of leukocytospermia and asymptomatic bacteriospermia is of no diagnostic value for the identification of men with acute bacterial infections and abnormal semen parameters, respectively. Reasons for this unexpected finding might be a possible delay in the deleterious actions of ROS produced by leukocytes due to their neutralization by antioxidants. Only once this neutralization capacity is depleted, these ROS will have a negative effect. On the other hand, even small amounts of bacteria can have a direct negative effect on sperm motility,^[17] yet this appears to depend on the type of pathogen.^[18] Furthermore, a number of studies provide evidence that bacteriospermia may further result in the deterioration of spermatogenesis, decreased sperm motility, altered acrosome reaction, altered morphology, formation of ROS leading to increased sperm nuclear DNA damage, formation of antisperm antibodies, and genital tract obstruction leading to inflammation and fibrosis.^[19-22] On the other hand, Esfandiari *et al.* pointed out that an asymptomatic leukocytospermia may be indicative of an early or “silent” genital tract infection.^[23]

Cytokines also play an imperative role in immunological and inflammatory mechanisms in response to host infections. These modulating agents are further grouped into five different groups among which interleukins (ILs) act by (i) modulating leukocytes to produce inflammatory response and (ii) by downregulating inflammatory cells.^[24]

Furthermore, they act to either induce or inhibit other cytokines, resulting in a network of cytokines to which cells respond.^[25] Thus, infiltrating pathogens stimulate the production of IL-8 by macrophages,^[26] which reportedly exerts a negative effect on the fertilizing potential of spermatozoa.^[27] Furthermore, infections often result in tissue damage which stimulates the generation of IL-1 and elicits further effects in the surrounding environment.^[28] IL-1 stimulates polymorphonuclear (PMN) neutrophils and macrophages to secrete IL-6, which in turn interacts with B-lymphocytes that ultimately become antibody-producing cells.^[29] These antibodies have been shown to be directed against invading pathogens and may further interfere with sperm function.^[30] Moreover, numerous studies have shown a correlation between decreased sperm function and seminal plasma with abnormally elevated levels of IL-6, IL-8, and tumor necrosis factor, all of which contribute to increased sperm cell membrane lipid peroxidation.^[31,32]

On the other hand, since most studies only investigated aerobic but not anaerobic bacteria, little is known about the impact of these pathogens which are also found in human semen.^[33,34] This may be due to the difficulty in culturing anaerobic organisms.

CLASSIFICATION OF URINARY AND GENITAL TRACT INFECTIONS

Clinically, urinary and genital tract infections are classified according to the nature of the microorganism and its clinical symptoms, which include (1) uncomplicated lower urinary tract infection (UTI), (2) uncomplicated pyelonephritis, (3) complicated UTI with or without pyelonephritis, (4) urosepsis, (5) urethritis, and (6) prostatitis, epididymitis, or orchitis.^[35] However, according to a preliminary study in 58 patients, it appears that the location (testes, epididymis, seminal vesicles, and prostate) of the infection has no influence on sperm functions in terms of motility or sperm DNA fragmentation. The levels of PMN-elastase were significantly higher only in patients with epididymitis or prostatitis, (Henkel *et al.*, unpublished).

It is estimated that more than one million sexually transmitted infections are acquired every day throughout the world, making these infections an imperative public health and socioeconomic concern.^[36] To date, the most prevalent sexually transmitted pathogens in uncomplicated UTI include *C. trachomatis*, *Ureaplasma urealyticum*, *N. gonorrhoeae*, and *Mycoplasma hominis*, with the exception of *Escherichia coli*. In 65%–80% of cases, *E. coli* is considered the most common cause of nonsexually transmitted urogenital tract infections, particularly in clinical entities such as epididymo-orchitis or prostatitis.^[3] In addition, a host of viral infections including mumps, human papillomavirus, herpes simplex virus, and human immunodeficiency virus, also contribute to increased leukocyte concentrations.^[37]

SEMEN CULTURES AND *CHLAMYDIA TRACHOMATIS*

C. trachomatis is an obligate pathogen with an intracellular (noninfectious, reproductive reticulate body) and an extracellular (infectious, toxin-releasing elementary body) form, which is responsible for 30%–40% of cases of urethritis. A study by Stamm has also shown that *C. trachomatis* results in the two most commonly sexually transmitted infections,^[38] causing urethritis in males and cervicitis in females. Globally, estimates by the WHO have shown that *C. trachomatis* accounts for 92 million urogenital tract infections per year,^[39] with asymptomatic presentations in 70%–80% of women and 50% of men. Furthermore, *C. trachomatis* has been detected in Leydig cells of the testis,^[40] prostate,^[41] and even epididymis and seminal vesicles,^[42] resulting in orchitis, prostatitis, epididymitis, and urethritis.

C. trachomatis infections in men may serve as reservoirs for transmission to females.^[43] Studies have also shown that *Chlamydia* sp. may be transported by leukocytes in semen, such as neutrophils and macrophages, which are more prevalent during an infection.^[44,45] Transmission between infected men and their sexual partners has been established,^[46] and partners of men with symptomatic urethral infection are more likely to be infected than partners of men with asymptomatic urethral infection.^[47] Therefore, both male and female partners should be tested if suspected of a sexually transmitted infection to treat the infection and improve the fertility outcome. The presence of antichlamydial antibodies in males is associated with the presence of infertility in female partners as well as the subsequent observed reductions in pregnancy rates.^[48] Moreover, *in vitro* studies by Hosseinzadeh *et al.* indicate that the pathogen directly elicits changes in the structure of sperm proteins and further induces premature cell death through lipopolysaccharides secreted by *Chlamydiae*.^[49]

Treatment modality

Treatment of *C. trachomatis* infections consists of a single oral dose of azithromycin (1 g) or doxycycline (100 mg taken orally twice a day), erythromycin base (500 mg taken orally four times a day), erythromycin ethylsuccinate (800 mg taken orally four times a day), levofloxacin (500 mg taken orally once), and ofloxacin (300 mg taken orally twice a day) for a period of 7 days. The prolonged administration of antimicrobials is required as *C. trachomatis* has a 48–72 h life cycle as they reside in the protective environment of epithelial cells. Therefore, early detection and treatment of asymptomatic infections are essential in preventing subsequent upper genital tract infections and its sequelae.^[50] Antibiotic treatment of *Chlamydia*- and *Ureaplasma*-related pyospermia resulted in significant improvements in sperm concentrations and progressive motility after 30 days. Yet, no significant effect could be observed for sperm viability.^[51]

SEMEN CULTURES AND *UREAPLASMA UREALYTICUM*

U. urealyticum, *M. hominis*, and *Mycoplasma genitalium* are pathogenic species which play an etiologic role in genital tract infections and are natural inhabitants of the male urethra which contaminate semen during ejaculation. Particularly, in the case of *U. urealyticum*, evidence of male infertility (incidence varying from 10% to 40%) caused by this pathogenic species has resulted in damage to the development and vitality of human embryos. The presence of *Ureaplasma* alone in semen or the female genital tract reduced the pregnancy rate per embryo transfer.^[52] The mechanism by which *U. urealyticum* affects sperm has not yet been established. However, numerous studies have shown that the presence of the pathogen in semen was related to a decline in sperm concentration,^[53,54] motility,^[55] morphology,^[56] higher semen viscosity, and a lower pH.^[54] In addition, higher seminal ROS levels and higher sperm DNA damage in response to *Ureaplasma* infection were also revealed.^[57]

Treatment modality

Treatment of *U. urealyticum* infections consists of a single oral dose of azithromycin (1 g single dose) or doxycycline (100 mg taken orally twice a day) for a period of 7 days.

SEMEN CULTURES AND *MYCOPLASMA HOMINIS* AND *MYCOPLASMA GENITALIUM*

M. hominis and *M. genitalium* are both associated with genito-UTIs^[58,59] accounting for 10.8% and 5% of the cases, respectively.^[60] *M. hominis* is often associated with nongonococcal urethritis, bacterial vaginosis, and postbirth fever^[61] while *M. genitalium* is an etiological agent of nongonococcal urethritis and nonchlamydial urethritis^[62] and may result in cervicitis^[63] and endometritis.^[64] Both species are capable of hampering reproductive outcome by attaching to and penetrating the human sperm plasma membrane,^[65,66] which in turn affects male fertility, the onset of pregnancy, and the possible health of offspring.

Treatment modality

Treatment of the *Mycoplasma* sp. consists of azithromycin (1 g single dose) or to improve efficacy, higher and longer courses of azithromycin (1.5 g course given as 500 mg on day 1 and then 250 mg daily on days 2–5), or azithromycin (two 1 g doses given 5–7 days apart), which is a less commonly used course of treatment.^[67–69] A recent study by Ahmadi *et al.* showed that the treatment of asymptomatic infection with *M. hominis* leads to improvement of semen parameters as determined by all semen parameters including total antioxidant capacity and ROS levels.^[70]

SEMEN CULTURES AND *NEISSERIA GONORRHOEAE*

In 2008, the WHO reported that the global incidence of *N. gonorrhoeae* was in excess of 106.1 million cases, with male patients typically presenting with lower urinary tract symptoms attributed to urethritis, epididymitis, and prostatitis in conjunction with a mucopurulent urethral discharge.^[71] Gonorrhea is spread through sexual contact or transmission during childbirth. A Gram stain of male urethral specimens that demonstrate PMN leukocytes with intracellular, Gram-negative diplococci can be considered diagnostic for infection in symptomatic men. In addition, the pili located on the surface of the bacterium facilitate attachment to other cells,^[72] which may bind to an asialoglycoprotein receptor in sperm that recognizes and adheres to lipopolysaccharides in gonococcal membranes.^[73]

Treatment modality

Treatment of *N. gonorrhoeae* infections consists of ceftriaxone (250 mg IM in a single dose) plus azithromycin (1 g taken orally in a single dose).^[51]

SEMEN CULTURES AND *ESCHERICHIA COLI*

E. coli are aerobic, Gram-negative bacilli and are the most common cause of nonsexually transmitted epididymo-orchitis, which contribute 65%–80% of the total cases of acute or chronic prostatitis in men.^[74] The deleterious effect of this pathogen on male fertility and specifically sperm quality is due to its effect on sperm motility^[75] and the impairment of acrosome reaction.^[76] The possible mechanism of sperm damage, in addition to the adhesion of pili, consists of the production of toxins and metabolic products stemming from bacterial proliferation. Two mechanisms by which bacteria affect spermatozoa were revealed by Schulz *et al.*^[77] and were described as a product of direct action and interaction of the soluble factors that induce apoptosis, resulting in a breakdown in the mitochondrial membrane potential.

Treatment modality

Treatment of *E. coli* consists of ciprofloxacin (250 mg taken orally daily for 3 days), norfloxacin (400 mg taken orally daily for 4 days), and trimethoprim–sulfamethoxazole (160–800 mg taken orally daily for 3 days).

CONCLUSION

Considering that infertility is a globally increasing problem with more couples recommended to turn to assisted reproduction, even with andrological factors such as mild asthenozoospermia, a thorough andrological diagnostic is essential to keep the cost and psychological stress of the patients at a minimum. Since male genital tract infections are often linked to poor sperm motility and function and

also remain “silent,” i.e., asymptomatic, this examination should also include a proper bacteriological testing of the semen including antibiotic resistance. By doing so, it is not only that a significant number of patients can be treated as infections are potentially treatable but also an appropriate antibiotic therapy can be selected. This in turn is crucial because transmission of the infection to the female partner must be avoided to increase the probability of fertilization and pregnancy as well as to eliminate possible illnesses of the offspring due to infection. However, using a semen culture as a screening test might be costly for patients. Therefore, a test makes only sense if there are clinical signs or other indications from the clinical picture of the patient.

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