Infectious, Inflammatory, and Immunologic Conditions Resulting in Male Infertility

Bassel G. Bachir, MD[a,b], Keith Jarvi, MD, FRCSC[a,b,c,d,*]

KEYWORDS

• Infections • Inflammation • Male infertility

KEY POINTS

- Reproductive tract inflammation is common in men with infertility and may be due to infections or noninfectious causes such as smoking, environmental toxins, vasectomy reversals, and urethral surgery.
- Although the presence of elevated levels of semen leukocytes is the most commonly used method to identify inflammation in the male reproductive tract, this is an inaccurate marker for inflammation.
- The use of empiric therapies such as antibiotics, antiinflammatories, and antioxidants may reduce semen leukocyte levels and improve sperm parameters for some infertile men with pyospermia.
- *Chlamydia trachomatis* and *Neisseria gonorrhoeae* screening for men with infertility is warranted in regions with a high prevalence of infection with these organisms.
- Viral infections, particularly human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) have been associated with male infertility.

INTRODUCTION

The accepted definition of infertility is the failure of a couple to achieve a successful pregnancy with 1 year of regular unprotected coitus. This condition is common, affecting almost 15% of couples worldwide, with a male factor implicated in up to 50% of cases.[1] A variety of conditions cause male infertility, including congenital malformations, exposure to environmental toxins, genetic and endocrinological disorders, and infectious and inflammatory conditions (the last condition accounting for almost 15% of cases of male infertility).[2] Inflammation is the body's response to a noxious agent in an attempt to eliminate it; the inflammatory response includes vasodilation, increased blood flow, and leukocytic infiltration to the infected site. The male reproductive organs that may be susceptible to infectious or inflammatory insults include the prostate, testicles, and epididymis, and with spermatogenesis and adequate sperm function intimately related to the proper function of these organs, any state of infection or inflammation may potentially impair the function of these organs and lead to altered sperm function, production, or transit. This review discusses the infectious and inflammatory conditions that are associated with male infertility and describes the biologic processes involved,

Funding Sources: None.
Conflicts of Interest: None.
[a] Division of Urology, Department of Surgery, University of Toronto, Toronto, Ontario, Canada; [b] Murray Koffler Urologic Wellness Centre, Mount Sinai Hospital, Joseph and Wolf Lebovic Building, 60 Murray Street, 6th Floor, Toronto, Ontario M5T 3L9, Canada; [c] Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada; [d] Lunenfeld-Tannenbaum Research Institute, Mount Sinai Hospital, Joseph and Wolf Lebovic Building, 60 Murray Street, 6th Floor, Toronto, Ontario M5T 3L9, Canada
* Corresponding author. Murray Koffler Urologic Wellness Centre, Mount Sinai Hospital, Joseph and Wolf Lebovic Building, 60 Murray Street, 6th Floor, Toronto, Ontario M5T 3L9, Canada.
E-mail address: kjarvi@mtsinai.on.ca

Urol Clin N Am 41 (2014) 67–81
http://dx.doi.org/10.1016/j.ucl.2013.08.008
0094-0143/14/$ – see front matter

which lead to impairment in fertility and sperm parameters.

INFLAMMATION—EFFECT ON THE MALE REPRODUCTIVE TRACT

Achieving normal fertilizing potential for the human male involves an intricate process of germ cell division and maturation, sperm transit through an elaborate maze of tubules, and the addition of fluids from accessory organs, allowing the germ cell to become fully functional.[3] Secretions by the prostate gland, seminal vesicles, and bulbourethral glands, including essential lubricants and products like zinc, citric acid, α-glucosidase, and fructose are crucial to attaining final normal sperm physiology. The completion of this delicate process described involves an intricate interplay between various organs with patent ducts: all these processes are unfortunately susceptible to various inflammatory and infectious insults (Fig. 1).

Inflammation is a complex process whereby the body reacts to infectious, traumatic, or chemical insults, causing an influx of activated leukocytes and various supporting cells and extracellular proteins.[3] Although chronic inflammation usually develops after an acute symptomatic insult, it may also occur in tissue without a known history of injury or insult. In fact, most men who have a genitourinary (GU) tract inflammation have no symptoms of this inflammation.

It is this latter insidious process that is most worrisome in the male reproductive tract. Evaluation of testicular tissue specimens from asymptomatic infertile men reveals leukocytic infiltration in greater than 50% of men.[4]

The impact of any inflammation or infection of the male reproductive tract on fertility depends on many factors, including the chronic versus acute nature of the disease and the type of invading pathogen (Fig. 2). However, noninfectious inflammatory reactions may also affect the male reproductive tract. Lymphocytic infiltrates are commonly observed in patients with testicular seminoma, others with carcinoma in situ, and even in the contralateral testis of patients with unilateral tumors.[5,6]

The inflammatory response is amplified by activated lymphocytes and macrophages through the release of cytokines, which includes a family of biologic response modifiers such as chemokines, interleukins, and growth factors.[7] The main mediators of the inflammatory response in the male reproductive tract are the proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1α, and IL-1β.[3] These signaling molecules are released by activated leukocytes and act in a synergistic fashion to allow cells to systematically eradicate the noxious insult. The cytokines IL-6, IL-8, and IL-10 are also released in states of inflammation and are found in varying levels in the semen of subfertile men with differing seminal defects, suggesting that semen cytokine profiling may potentially be used to detect inflammation in the male reproductive tract and may possibly help more accurately categorize subfertile men to aid in future treatment.[8,9] Furthermore, IL-6 levels were also found to be elevated in patients with nonpathogenic inflammation, also suggesting its use as a marker of this condition.[10]

Inflammation of the testicles may lead to spermatogenic arrest and a decrease in serum levels of testosterone and luteinizing hormone, thereby affecting the dual functions of spermatogenesis and steroidogenesis.[3,11] The secretion of both TNF-α and IL-1α during the inflammatory response

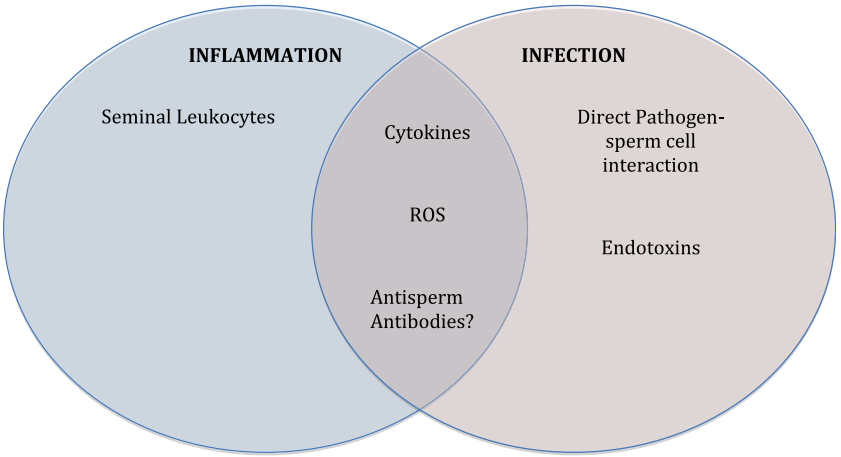

Fig. 1. Synergistic effect of inflammation and infection leading to male reproductive tract dysfunction and/or obstruction.