



CME review

Immunologic disorders of the female and male reproductive tract

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- Describe the clinical immunologic disorders of the female and male reproductive tracts that are most likely to be encountered in clinical practice

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Introduction

The male and female reproductive tracts depend on innate immune responses, including surface defenses, cytokine responses, complement activation, and phagocytic cell responses, to protect against external insults, such as microbial infection. However,

when these natural protective responses are compromised, a spectrum of problems can arise, including infection, autoimmunity, infertility, and hypersensitivity disorders. For example, when the sterile portion of the female genital tract is compromised, infection can ensue, leading to inflammation and tissue remodeling.¹ Similarly, when the blood-testis barrier in the male reproductive tract is compromised, interaction between intragenital and extragenital tract components increases the risk of spermatozoa autoantibodies.² This review examines aspects of innate and adaptive immu-

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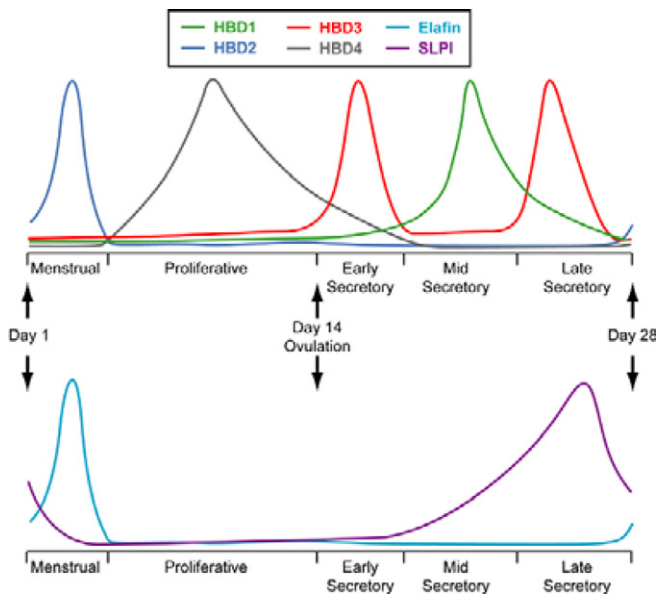


Figure 1. Peak expression of β -defensins, human β -defensins (HBDs) 1 through 4, natural antimicrobial proteins, secretory leukocyte protease inhibitor (SLPI), and elafin in the endometrium throughout the menstrual cycle. HBD1, HBD3, and SLPI are maximally expressed during the secretory phase, HBD4 is highest in the proliferative phase, and HBD2 and elafin peak during menstruation. Reproduced from King et al.⁴

nity in the female and male reproductive tracts and describes some of the autoimmune and hypersensitivity clinical disorders that can develop when these pathways are compromised. We performed a search of the literature from PubMed to identify immunologic disorders of the male and female reproductive tracts. Relevant studies addressing the innate and adaptive immune responses in the female and male reproductive tracts were chosen for this review.

Female and Male Innate Immune Responses

The sterile upper female genital tract includes the fallopian tubes, uterus, and cervical plug, whereas the nonsterile lower female genital tract includes the ectocervix and vagina.¹ The lower genital tract must have an efficient innate immune system to eliminate harmful microbial agents and other contaminants to protect the host from overwhelming infection.³ Natural antimicrobial peptides (NAPs), pattern recognition Toll-like receptors (TLRs), defensins, complement, and effector natural killer (NK) cells are all constituents of the innate immune response that work in concert to protect the host from external threats.^{1,4}

NAPs include the whey acidic protein motif containing proteins, secretory leukocyte protease inhibitor (SLPI), and elafin, which prevent host tissue damage by inhibiting proteases released by gram-negative and gram-positive bacteria.^{1,4} By preventing unnecessary damage to host tissue, NAPs can reduce the host's susceptibility to microbial colonization and infection. Proteases inhibited by SLPI include neutrophil elastase, trypsin, and cathepsin G, whereas elafin inhibits neutrophil elastase and proteinase 3.¹ The NAPs are found in highest concentration within the cervical mucus and vagina, where bacterial contamination is greatest. In vitro stimulation of endocervical and vaginal cell lines with lipopolysaccharide leads to increased NAPs.¹ Levels of NAP fluctuate during the different menstruation phases but peak during the progesterone-dependent secretory phase (Fig 1).⁴ The SLPI increases during the first trimester, at term pregnancy, and at onset of labor in the uterine decidua and amniotic fluid, whereas elafin is localized to the amnion epithelium, decidua, chorion, and placental trophoblast.⁴ Both play an important role in preventing microbial invasion during pregnancy.⁴

Defensins are small cationic proteins divided into α - and β -groups based on disulfide bond positions that have antibacterial, antifungal, and antiviral properties important for host protection.^{1,4} The α -defensins are found in neutrophils (human neutrophil peptides 1–4) and on epithelial surfaces (human α -defensins 5 and 6), whereas human β -defensins (HBD) are found primarily on epithelial surfaces (HBDs 1–6).^{1,4} Human β -defensins are constitutively expressed (HBD1) or induced after challenge with an inflammatory or infectious stimulus.^{1,4} The chemoattractant properties of β -defensins facilitate interaction between the innate and adaptive immune responses. Defensin levels also fluctuate during the menstrual cycle (Fig 1).⁴

The TLRs recognize pathogen-associated molecular peptides, microbial-associated molecular peptides, and danger-associated molecular peptides. They are ubiquitously expressed, including the endometrium, cervix, fallopian tubes, and epithelial cells.^{1,5} Their presence on uterine NK cells suggests an important role during implantation and early pregnancy.¹ The TLRs respond to different ligands, resulting in increased cytokine and chemokine production and leading to increased chemotaxis of monocytes and neutrophils into surrounding tissue.^{1,5} Figure 2 illustrates the interaction among TLRs, defensins, and NAPs in regulating the innate immune response.¹

Complement activation also plays an important role in protecting the host from infection.⁶ Effector NK cells are the major lymphocyte in the pregnant decidua that promote immunologic tolerance important for protecting the fetus from infection.⁷ Mast cells are increased in the endometrium of patients with endometriosis and during blastocyte implantation, but their role in the innate immune response is still unclear.⁸

Male innate immune responses are most pronounced in the ejaculate because protecting spermatozoa from harsh external environments is essential. The male ejaculate is formed from secretions primarily from the seminal vesicles (1.5–2 mL), prostate (0.5 mL), and Cowper gland and gland of Littre (0.1–0.2 mL).⁹ Seminal plasma contains high concentrations of potassium, zinc, citric acid, fructose, phosphoryl choline, spermine, free amino acids, prostaglandins and prostate-specific antigens (PSAs), and enzymes (eg, phosphatase, diamine oxidase, β -glucuronidase, lactic dehydrogenase, α -amylase, lysozyme, plasminogen activators, and pepsinogen), which are all important for supporting a healthy environment for spermatozoa.⁹ Zinc binds to several different proteins, including PSA, and when absent affects sperm chromatin stability, leading to decreased fertility.¹⁰ Zinc also serves as a prostate antibacterial factor due to its broad antibactericidal activity.¹¹

Prostaglandins, primarily derived from seminal vesicles, have strong stimulatory and inhibitory effects on smooth muscle important for controlling erection, ejaculation, sperm motility, and transport. Prostaglandin E₂ (PGE₂) can modify dendritic cell function by affecting their differentiation, maturation, and migration. PGE₂ also increases dendritic cell capacity to produce higher levels of proinflammatory cytokines/chemokines, express higher levels of major histocompatibility complex (MHC) class II molecules and TLRs, and activate the nuclear factor κ B signaling pathway. All of these functions are important for regulating tissue inflammation.^{12–14}

PSA, a serine kallikrein protease with chymotrypsin- and trypsin-like activity, may be important in initial clotting and subsequent lysis of clotted ejaculates and is an important marker for monitoring prostate cancer.⁹ It also activates peripheral blood mononuclear cells, resulting in secretion of interferon γ (IFN- γ) by NK cells.¹⁵ Semenogelin, a seminal vesicle secretory protein, serves as a substrate for PSA. Although, the mechanisms of semenogelin's action and its targets are still unknown, its improper degradation decreases fertility by reducing sperm motility.¹⁶ Experimental evidence indicates that PSA rapidly cleaves semenogelin, leading to semen liquefaction and initiation of sperm motility.¹⁶

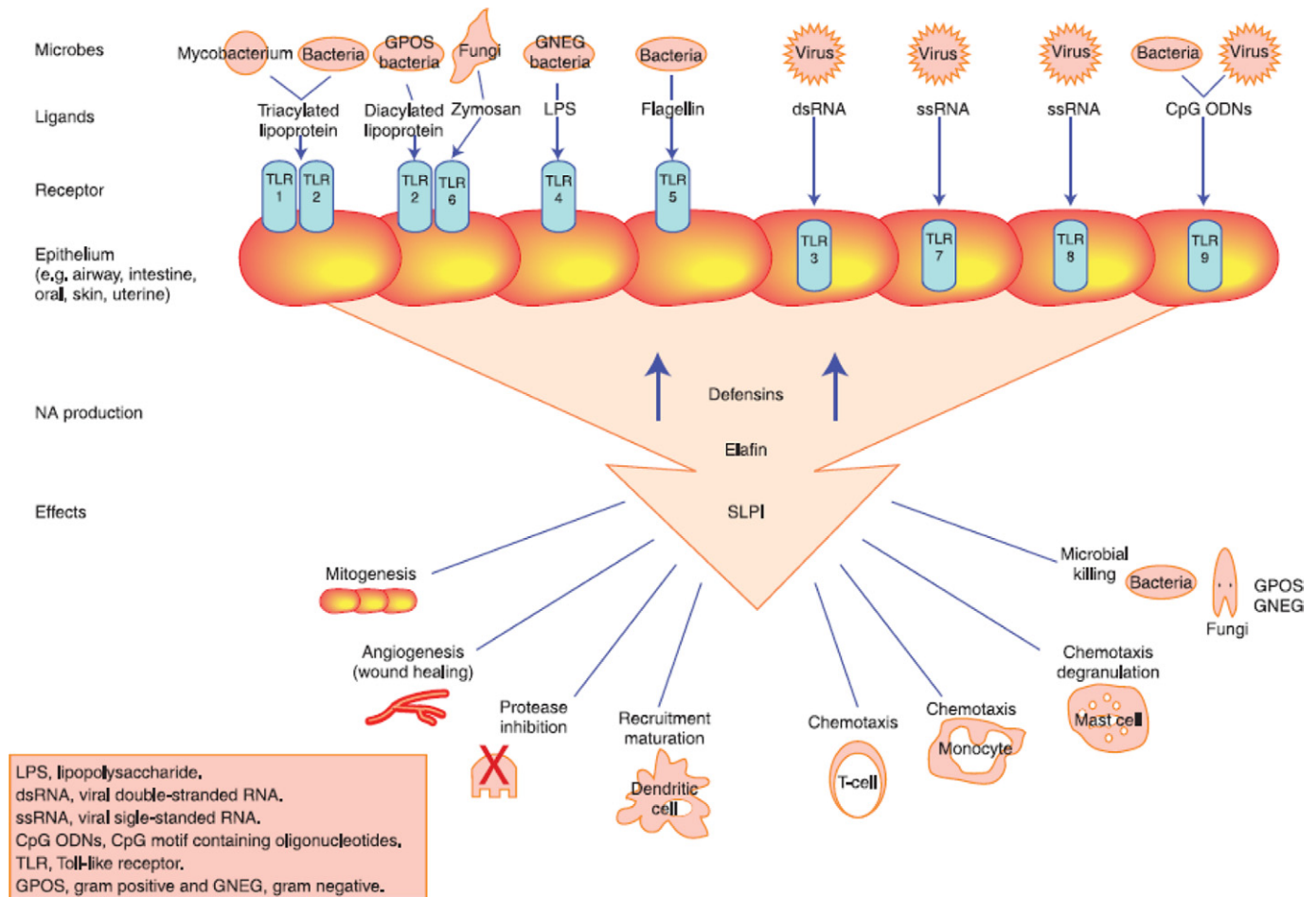


Figure 2. Cellular origin, target cell lineage of natural antimicrobial peptides, defensins, and Toll-like receptors. Reproduced from Horne et al.¹

Human seminal plasma contains measurable levels of IgG (7–22 mg/dL), IgA (0–6 mg/dL), and C3 complement (1.82 mg/dL). These levels increase 10-fold in patients with prostatic adenocarcinoma.⁹

Female and Male Adaptive Immune Responses

Unlike the gastrointestinal tract, where antigen can be processed by lymphoid tissue within Peyer patches, the genital tract does not have organized lymphoid tissue.¹⁷ Lymphoid aggregates have been reported in the uterus but fluctuate with menstruation.¹⁷ The female genital tract possesses antigen-presenting cells, such as macrophages, dendritic cells, and epithelial cells, that constitutively express MHC class II molecules, which are under strong hormonal control.¹⁷

Because of the close proximity of the vagina to the rectum, the vagina has had to develop an effective system for containment and/or efficient elimination of pathogens. This is in part due to the high concentrations of NAPs and defensins found in the nonsterile vagina and cervical regions, making them hyporesponsive to pathogens.¹ In contrast, the endocervical, uterine, and fallopian tube epithelia can elicit site-specific immune responses, leading to increased cytokine and chemokine responses that help prevent infection and provide protection during egg implantation and pregnancy.¹⁷ Pathogens in conjunction with hormones can influence the genital microenvironment by either favoring induction of immunity or promoting viral invasion. For example, human immunodeficiency virus (HIV) 1 variants use the CCR5 chemokine coreceptor to facilitate infection. Women taking oral contraceptives, which have been demonstrated to increase expression of CCR5 on CD4 cells, may therefore be at increased risk for viral transmission.¹⁷

Cell-mediated immune responses are important for protecting the female from sexually transmitted diseases.¹⁸ Antibody-dependent, cell-mediated cytotoxicity of Chlamydiae-infected epithelial cells may provide anti-HIV protection in humans.¹⁸ Furthermore, specific CD8 T cells in the cervix of HIV-infected women may function as specific cytotoxic T cells or by producing IFN- γ that promote antiviral activity.¹⁸ Women with pelvic inflammatory disease or recurrent *Chlamydia trachomatis* infections have reduced IFN- γ production in response to chlamydial heat shock protein 60 (HSP60) not seen in women with fewer infections or infertility due to other causes.^{18,19} Genital tract infections with Chlamydiae appear to be associated with interleukin (IL) 10-producing regulatory T cells, whereas T_H1 cells appear to be protective.^{12,18}

In the male reproductive tract, most T cells are CD8 suppressor/cytotoxic cells located along with macrophages in the epithelium and lamina propria of the vas deferens, epididymis, and rete testes.² IFN- γ -producing activated T cells are potent inducers of MHC class II antigen expression on antigen-presenting macrophages.² Several mechanisms exist to inhibit this IFN- γ -induced immune response. Increased numbers of CD8⁺ T cells presenting along regions where the blood-testis barrier is weakest may act to suppress immune responses to sperm specific antigens.^{2,20} In contrast, increased CD4⁺ lymphocytes are present in the genital tract and semen of men with spermatozoa autoantibodies.²⁰

Spermatozoa autoantibodies can result from testicular trauma, inflammation from infectious or noninfectious causes, congenital anomalies, or secondary to vasectomy.² Spermatozoa bound with autoantibodies are potent inducers of IFN- γ . Women who have husbands with spermatozoa autoantibodies have increased se-

rum IFN- γ levels compared with women whose husbands do not have autoantibodies.²¹ Of interest, T $\gamma\delta$ cells comprise up to 33% to 50% of T cells in the human semen compared with less than 10% of T lymphocytes in the peripheral blood and are further increased in men with spermatozoa autoantibodies or a *C trachomatis* infection.² The functional role of increased numbers of T $\gamma\delta$ cells in the male genital tract is still unclear and requires further exploration.^{2,22}

Heat shock proteins, produced in response to microbial infection and inflammation, are also important for down-regulating proinflammatory immune responses.¹⁹ They work by preventing intracellular protein degradation and incorrect polypeptide assembly and by inhibiting macrophage production of IL-1 and tumor necrosis factor α (TNF- α).² HSP60 is present in semen from men with chlamydial infections or spermatozoa autoantibodies but absent in semen from men without these immune-activating responses.¹⁹ T $\gamma\delta$ cells' ability to induce HSP gene expression and synthesis of HSP, which in turn can activate T $\gamma\delta$ cells, demonstrates their important interrelated role of down-regulating pro-inflammatory responses in the male genital tract.^{2,19}

Clinical Conditions Involving the Female and Male Genital Tracts

Relatively few autoimmune disorders primarily affecting the female and male reproductive tracts have been previously described. Reactive arthritis typically occurs after a genitourinary or gastrointestinal tract infection.²³ The classic triad of reactive arthritis syndrome is nongonococcal urethritis, conjunctivitis, and arthritis.²³ Men are affected more than women, and most express HLA B27. Men experience dysuria, mucopurulent urethral discharge, prostatitis, and epididymitis.²³ Women experience dysuria, vaginal discharge, purulent cervicitis, and/or vaginitis. Some patients have asymptomatic genital inflammation associated with sterile pyuria.²³ *C trachomatis* is the most common cause of urethritis or cervicitis; however, *Neisseria gonorrhea* can occur in conjunction with *Chlamydia* infections.²³ The immunopathogenesis of reactive arthritis syndrome is unclear but likely due to immune responses induced by *Chlamydia* and other microbial infections. Extra-articular manifestations include mucocutaneous lesions of the nails, mouth, and skin, fever, weight loss, uveitis, aortitis, and amyloidosis.²³ Diagnosis is based on clinical history and laboratory findings. The presence of seronegative, asymmetrical oligoarthritis in a young person should alert the clinician to possible reactive arthritis syndrome. This condition is usually self-limiting for 1 year but can result in residual musculoskeletal symptoms and relapse in 15% of patients.²³ Approximately 15% of patients have chronic, destructive arthritis and vision loss, whereas 10% develop ankylosing spondylitis. Mortality, although rare, can occur from cardiac complications or amyloidosis.²³

Behçet disease is an inflammatory disorder of unknown cause that involves multiple organ systems. Recurrent episodic oral and genital ulcerations (scrotal and penile in men and vulvar and cervical in women) are the most common presentation.²⁴ Uveitis occurs months to years after onset. Approximately half of patients experience large joint synovitis during an acute attack.²⁴ The presence of increased circulating CD8⁺ $\gamma\delta$ T lymphocytes suggests that exposure to microbial antigens may be a contributing factor in genetically predisposed individuals (ie, HLA-B51).²⁵ Treatment includes corticosteroids, azathioprine, chlorambucil, cyclophosphamide, cyclosporin A, IFN- α , or TNF- α agents. Behçet disease is characterized by relapses and remissions. Prognosis depends on which organ systems are involved. Loss of vision and neurologic disease are major causes of morbidity and disability.²⁴

Candida vulvovaginal infections occur in 75% of the female population.²⁶ Recurrent infections occur more commonly in diabetic patients and in conjunction with taking oral contraceptives or an-

tibiotics, but most women have no recognizable risk factors.²⁶ Topical or oral antifungal agents are usually effective, but 5% of women experience recurrent *Candida* infections after treatment.²⁶ Little research has been performed to investigate the pathogenic mechanisms and treatment of recurrent vaginal *Candida* (RVC) infections. Meech et al²⁷ suggested that IgE- and/or cell-mediated hypersensitivity mechanisms are involved. Witkin et al²⁸ demonstrated that some women with RVC have abnormal macrophage responses to *Candida albicans*, resulting in increased PGE₂, which inhibits lymphocyte responses to *Candida* antigen. Anti-*Candida* IgE antibodies and PGE₂ in vaginal fluid of many women with RVC infections suggests that vaginal hypersensitivity *C albicans* may be caused by increased levels of PGE₂, which can suppress localized vaginal cell-mediated immune responses, resulting in *Candida* yeast colonization and recurring infections.^{26,29,30}

Several women with vulvovaginal *Candida* hypersensitivity manifesting as RVC infections have been successfully treated with *Candida* desensitization.^{31,32} Although still considered controversial, a study by Rigg et al³² treated 18 women experiencing RVC infections who were sensitized to *C albicans* with *Candida* immunotherapy. Most (79%) experienced a decrease in the mean $\pm$ SD number of vaginitis episodes (17.2 ± 2.0 to 4.3 ± 1.8 ; $P < .0004$) after 1 year of treatment.³² The investigators concluded that *C albicans* immunotherapy appeared effective, but double-blinded, placebo-controlled trials were needed to verify their results.³²

Insight into the underlying mechanism(s) of chronic vulvovaginal *Candida* hypersensitivity comes from mouse models that suggest that innate and adaptive immune responses are required to protect the host from systemic *Calbicans* overgrowth.^{26,28,29} Within the vaginal mucosa, a fine balance between T_H1 and T_H2 responses and other bioactive mediators prevents RVC and subsequent hypersensitivity reactions from occurring.^{33,34} Finally, it is important to emphasize that women with RVC have significant emotional distress because this condition significantly interferes with having normal interpersonal relationships.

Human seminal plasma hypersensitivity (SPH) can manifest as localized vaginal and/or systemic anaphylactic reactions.^{35–37} Women with systemic SPH experience diffuse urticaria and facial, tongue, lip, and throat angioedema with and without stridor, wheezing, diarrhea, and in the most extreme situations vascular collapse, whereas women with localized SPH experience immediate postcoital vulvovaginal burning and pain that persists for hours, days, or weeks.^{26,37} The prevalence of SPH is unknown in the general population, and death from this disorder has not been reported. A questionnaire study of women with suspected SPH revealed 88 of 1,073 respondents (8%) had symptoms consistent with probable SPH.^{26,37} Extrapolation of this figure to the US population suggests approximately 20 to 40,000 women could have this condition.³⁷ Avoidance of semen is effective but not acceptable to women desiring a normal sexual relationship and/or who want to conceive naturally.^{26,37} Untreated SPH often results in significant emotional strain on interpersonal relationships.^{26,37}

The onset of SPH is between 20 and 30 years of age.^{37–39} Localized SPH reactions appear more commonly but are often associated with systemic symptoms.³⁹ Neither atopy nor promiscuity is a risk factor for SPH.^{37,39} Interestingly, onset of symptoms occurs after first intercourse in approximately 30% to 40% of cases.^{37,39} Symptoms begin within seconds to minutes after seminal fluid contact and can last several hours.^{37,39} A sentinel feature of SPH is that condoms donned before coitus prevents symptoms.^{37,39} Desensitization to relevant seminal plasma proteins is effective for systemic and localized SPH.^{35,36} Because of the potential inhibitory effect by high-molecular proteins on lymphocyte cell-mediated responses, gel column fractionation is recommended to remove these proteins before treatment.⁴⁰

PSA, a 31-kDa glycoprotein, is believed to be the major allergen causing SPH, but other allergens might be involved.^{26,41–43} Dog PSA has significant cross-reactivity with human PSA.⁴¹ Therefore, women experiencing symptoms after first intercourse with prior exposure and sensitization to Can f 5 (dog kallikrein PSA) may be experiencing a cross-reactive reaction with human PSA.^{41,44}

In 1991, Gulf War veterans reported burning of their semen after ejaculation, which in some cases caused localized vaginal burning, pain, and swelling in their female sexual partner.⁴⁵ This condition, called burning semen syndrome (BSS), resembled localized SPH reported in the civilian population.^{36,45} Questionnaire surveys distributed to 188 male Gulf War veterans suspected of having BSS from 41 states, Puerto Rico, Canada, and the United Kingdom revealed that 7% of respondents had preexisting symptoms before the Gulf War and less than 50% of their sexual partners experienced resolution of symptoms with a condom, excluding localized SPH.⁴⁵ Interestingly, several male veterans had positive skin test results to their seminal plasma proteins.⁴⁵

Dividing respondents into “healthy” and “unhealthy” groups based on absence or presence of multiple physical symptoms revealed a significant correlation between posttraumatic stress disorder and the unhealthy group.⁴⁵ Five Gulf War couples from the “healthy” group who met criteria for systemic or localized SPH were treated with seminal plasma protein desensitization.^{35,36,45} Three couples had complete response to treatment, 1 had partial improvement, and 1 had no response.⁴⁵ In general, BSS evaluation was hindered by poor case definition of the underlying problem, multiple concomitant somatic and psychological symptoms hindering a focused evaluation, and logistical difficulties in evaluating geographically dispersed individuals during the study.⁴⁵ Although the pathogenesis of BSS was not identified, it is plausible that external environmental insults disrupted innate immune responses in the male seminal fluid, which subsequently interfered with protective vaginal immune responses in the female genital tract, leading to a T_H2 hypersensitivity immune response.⁴⁵

In 2002, men experiencing severe fatigue, low-grade fevers, nasal congestion, burning eyes, concentration difficulties, irritability, and flulike symptoms occurring after ejaculation were described.⁴⁶ This condition was termed postorgasmic illness syndrome (POIS). Criteria for establishing a diagnosis of POIS based on demographic characterization of 45 men with this condition include the following: (1) a flulike state, extreme fatigue or exhaustion, muscle weakness, mood disturbances/irritability, memory/concentration difficulties, incoherent speech, nasal congestion, rhinorrhea, and itching eyes; (2) immediate or slightly delayed onset of symptoms after ejaculation; (3) occurrence in more than 90% of ejaculation events; (4) duration for 2 to 7 days; and (5) spontaneous resolution.^{47,48} Reactions are speculated to be the result of an autoallergic reaction to the male's own semen involving IgE and cell-mediated immune responses.^{47,48} Successful desensitization of 2 men using their own semen was reported.⁴⁷ However, the risk of the male subjects developing spermatozoa autoantibodies using this approach has not been adequately addressed. Further investigation of POIS is warranted because it appears to be affecting growing numbers of men.

Conclusion

The immunology of the female and male genital tracts is a complex network of interactions designed to protect the host from microbial infection and immunogenic responses to self- or exogenous antigens. The immunology of the reproductive tract is rapidly evolving, but the pathogenesis of the primary clinical disorders described in this review is still poorly elucidated, emphasizing the need for further research. However, the reproductive tract represents an excellent model for investigating the interaction between

external environmental factors and localized mucosal immune responses, leading to disease.

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