

Seminal Plasma Hypersensitivity Reactions: An Updated Review

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ABSTRACT

Seminal plasma hypersensitivity manifests as a spectrum of systemic and/or localized clinical symptoms after exposure to specific protein components in seminal fluid. The prevalence of this disease is largely unknown, but it is believed to affect up to 40,000 women in the United States. Although no definitive risk factors have been confirmed, women with systemic reactions are frequently atopic. Prostate-specific antigen is believed to be the major allergen involved in the disorder, but other proteins are likely involved. Interestingly, up to 40%–50% of both systemic and localized seminal plasma hypersensitivity cases can occur after first-time intercourse. Diagnosis is based on clinical history. The gold standard for diagnosing seminal plasma hypersensitivity is prevention of symptoms with the use of a condom. Patients with seminal plasma hypersensitivity demonstrate positive prick skin test and/or serum-specific immunoglobulin E to whole seminal fluid or fractionated seminal plasma proteins. Treatment of seminal plasma

hypersensitivity involves either avoidance with the use of condoms, intravaginal graded challenge using dilutions of whole seminal fluid, or subcutaneous desensitization to relevant fractionated seminal plasma proteins obtained from the woman's sexual partner. In most cases, treatment using one or more of the above approaches has been very successful. Infertility has not been demonstrated to be directly related to seminal plasma hypersensitivity, although women with the condition frequently have difficulty conceiving due to their inability to have unprotected sexual intercourse. **Mt Sinai J Med 78:803–809, 2011.** © 2011 Mount Sinai School of Medicine

Key Words: dyspareunia, prostate-specific antigen, seminal plasma hypersensitivity, seminal plasma proteins.

Seminal plasma hypersensitivity (SPH) was first reported by a Dutch gynecologist, J. L. H. Specken, in 1958.¹ Since that time, numerous cases of human seminal plasma (HSP) hypersensitivity have been described in the literature.^{2–4} Seminal plasma

Seminal plasma hypersensitivity manifests as a variety of systemic and/or localized clinical symptoms after exposure to specific protein components in seminal fluid. Women who present with localized seminal plasma hypersensitivity reactions develop immediate postcoital vulvovaginal burning, pain, redness, and labial swelling sometimes associated with formation of vesicles. Systemic symptoms can occur with or without localized pelvic and vulvovaginal pain.

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hypersensitivity manifests as a variety of systemic and/or localized clinical symptoms after exposure to specific protein components in seminal fluid.^{1,5,6} Women with systemic SPH can present with a spectrum of symptoms including diffuse urticaria; facial, tongue, lip, and/or throat angioedema; stridor; wheezing; dyspnea; abdominal, pelvic, and/or vulvovaginal pain; and swelling, nausea, vomiting, diarrhea, general malaise, hypotension, or, in rare cases, loss of consciousness and complete circulatory failure. Women who present with localized SPH reactions develop immediate postcoital vulvovaginal burning, pain, redness, and labial swelling sometimes associated with formation of vesicles. Systemic symptoms can occur with or without localized pelvic and vulvovaginal pain. Systemic reactions typically occur within 30 minutes postcoitally after exposure to SPH but can be delayed in onset over 2–3 hours and typically resolve over a 24-hour period or sooner after treatment with antihistamines.⁶ For localized reactions, vaginal pain and malaise may persist for several days to weeks.^{1,3,6–8}

Avoidance of semen, although an effective solution, is usually not an acceptable lifestyle change by women desiring to have a normal sexual relationship and/or wanting to conceive. Seminal plasma hypersensitivity is a serious clinical dilemma for these women, as it frequently causes significant emotional strain on marriages and relationships.¹

MECHANISM

Seminal plasma contains high concentrations of potassium, zinc, citric acid, fructose, phosphoryl choline, spermine, free amino acids, prostaglandins, and enzymes. The major enzymes in seminal plasma are acid phosphatase, diamine oxidase, β -glucuronidase, lactic dehydrogenase, α -amylase, lysozyme, plasminogen activators, pepsinogen, prostate-specific antigens (PSA), and other seminal proteinases. The prostate is the major source for most of these proteins.⁹

Previously, investigators have reported the immunosuppressive effects of seminal plasma proteins (SPP) and spermatozoal proteins. Lord *et al.* demonstrated that SPP had a suppressive effect on cellular immunity using mixed lymphocyte reactions and mitogen induced lymphocyte blast transformation assays.¹⁰ Marcus *et al.* found spermatozoan proteins suppressed mitogen-induced lymphocytic responses in a dose-dependent fashion while performing a series of experiments to investigate the correlation between infertility and

antisperm antibodies.^{11–15} Subsequently, several fractionated SPP were also found to inhibit lymphocyte proliferation.¹¹ This seminal plasma immunosuppressive factor has been speculated to be important for suppressing local immune responses to spermatozoa in the female reproductive tract and may also explain why women treated by intravaginal challenge using whole seminal plasma fluid often do not respond therapeutically.

Currently, the most relevant sensitizing protein in patients with SPH is believed to be PSA, a 33–34 kD glycoprotein, although other proteins yet to be well characterized may also be involved.^{16,17}

Currently, the most relevant sensitizing protein in patients with seminal plasma hypersensitivity is believed to be prostate-specific antigen, a 33–34 kD glycoprotein, although other proteins yet to be well characterized may also be involved.

It has been proposed that a common protein cross-reacting with PSA may explain the high incidence of cases occurring after first time intercourse. Recently, a prostatic kallikrein protein isolated from dog urine and epithelial extract was reported to be >80% structurally homologous to human PSA.^{18,19} Investigators have postulated that women who experienced SPH after first-time intercourse could have become sensitized to prostatic kallikrein through previous exposure to dogs.^{18,19} However, this hypothesis has yet to be proven and our unpublished observations have not found any correlations between dog ownership, exposure, or sensitization and localized or systemic SPH.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

At present, the prevalence and incidence of SPH is unknown. A previous review of SPH cases in the literature described 32 cases reported between 1958 and 1989.³ Of these cases, the time of onset of symptoms for 18 patients began between 20 and 30 years of age. The majority (27 of 32) of these women reported dermatitis, urticaria, and pruritis. Anaphylaxis was reported in 22% of cases, and 40% of cases experienced symptoms after first-time intercourse.³

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In a subsequent larger questionnaire-based study of 1073 women who suspected they had symptoms consistent with SPH, 130 women were determined to have probable SPH based on their questionnaire responses.⁷ Women were considered “probable” for SPH if they reported ≥ 2 symptoms consistent with localized and/or systemic SPH and complete prevention of symptoms with the use of a condom. Of the 130 women with probable SPH, 46 (35%) reported localized symptoms and 84 (65%) reported systemic symptoms. The mean age of onset was 24 and 23 years, respectively, for localized and systemic reactors. Onset with first-time intercourse was reported in 43.4% for localized reactors and 20.2% of systemic reactors.

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The average number of sexual partners for localized and systemic reactors was 1.7 and 1.4, respectively. A history of atopy was reported in 50.7% of women with probable SPH. Although this retrospective survey does not provide definitive prevalence data on HSP hypersensitivity, it was extrapolated from the questionnaire response rate and the number of women with probable SPH that 20,000–40,000 women in the United States could potentially have this condition.⁷

DIFFERENTIAL DIAGNOSIS

The diagnosis of SPH requires the exclusion of other underlying disorders that may have similar clinical presentations. The differential diagnosis of SPH is summarized in Table 1. Conditions that should be considered for women presenting with these symptoms include allergic vulvovaginitis, vaginal contact dermatitis, chronic vulvovaginalcandidiasis, latex hypersensitivity, food or drug reactions as the result of proteins and/or metabolites being transmitted via the male’s seminal fluid to the female with an existing history of sensitization to that food or drug, sexually transmitted diseases (STD; viral and/or bacterial), exercise or

Table 1. *Differential Diagnosis of Human Seminal Plasma Hypersensitivity.*

Allergic vulvovaginitis
Chronic vulvovaginal candidiasis
Seminal plasma fluid transfer of a drug or drug metabolite
Seminal plasma transfer of food allergens
Infection
Contact dermatitis (latex, lubricants, spermaticides)
Structural problems (small vaginal introitus)
Exercise or vibratory angioedema
Irritant reactions (scented toilet tissues, soaps)

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vibratory induced urticaria/angioedema, and physical factors, such as a small introitus.^{6,20–29}

CLINICAL EVALUATION

The medical history is essential for making an accurate diagnosis of SPH as it allows formulation of a complete differential diagnosis. Many of the questions asked are available online at <http://www.seminalplasmaallergy.org>. An important question to ask all patients suspected of having SPH is whether condoms completely prevent symptoms. It is important to ask the patient whether or not the condom was donned before intercourse or just prior to ejaculation, as there can be leakage making it appear that condoms were ineffective.

Blood and other laboratory testing, to rule out other conditions that can manifest as SPH, should be performed on the female and the male sexual partners.

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A pap smear, candida culture, KOH prep, and vaginal cultures for bacteria and viruses, including herpes simplex virus culture and a human papillomavirus DNA probe should be performed to exclude STDs, bacterial vaginitis, and vulvovaginal candidiasis. Both the patient and partner should have an enzyme-linked immunosorbent assay (ELISA) human immunodeficiency virus screening test. For systemic reactors, a complete blood count with differential, renal panel, liver panel, thyroid-stimulating hormone, complements 3 and 4, and antinuclear antibody should be obtained from the patient to rule out other causes of angioedema and urticaria. Only after other potential causes, especially infectious, have been eliminated should the workup of SPH proceed.

The initial step in evaluating a patient suspected of having SPH is to first obtain a fresh ejaculate from their spouse or sexual partner. The sample should liquefy at room temperature for 30 minutes, and then be centrifuged at 5000 g for 10 minutes to separate the spermatozoa from the seminal fluid. The supernatant, which contains the seminal fluid proteins, is used for skin prick testing.

Following centrifugation, the supernatant of a fresh ejaculate, which contains the seminal fluid proteins, is used for skin prick testing.

It is recommended that the spouse or sexual partner also be tested as a negative control to ensure there is no irritant response. Intracutaneous testing to whole seminal fluid is not recommended due to known irritant reactions. A false-negative test can occur if the patient is taking antihistamines or other medications that block an H1 receptor response or

secondary to a dilutional effect, as whole seminal fluid contains numerous proteins, many of which are not relevant allergens.³⁰

Commercial assays exist for testing specific immunoglobulin E (IgE) antibodies to seminal fluid proteins, but the positive and negative predictive values of these assays are not well delineated. A positive skin prick test response to the subject's sexual partner's whole seminal fluid with confirmation utilizing serum-specific IgE ELISA or western immunoblot to whole SPP has a high positive predictive value for a successful therapeutic response to SPP desensitization.^{2,7,31-36}

Column fractionation to separate the SPP by molecular weight is required to isolate individual proteins for skin prick testing and, if necessary, intracutaneous testing which when isolated are less irritating. These fractionated proteins can subsequently be used for treatment. Because of the potential

Column fractionation to separate the seminal plasma proteins by molecular weight is required to isolate individual proteins for skin prick testing and, if necessary, intracutaneous testing which when diluted are less irritating.

inhibitor effect on lymphocyte cell-mediated responses of high molecular proteins and/or a dilutional effect of using whole seminal fluid, gel column fractionation allows separation of the SPP and removal of the large molecular weight proteins before testing and/or immunotherapy. Aseptic technique is utilized during the fractionation process. The resulting protein fractions undergo bacterial, fungal, and viral culture for 7 days to ensure a sterile product and then are Millipore filtered prior to use for skin testing and subcutaneous desensitization. The female and her spouse or sexual partner are tested to all of the isolated SPP to determine which one(s) are sensitizing. Skin prick testing is performed using the neat concentration of each SPP and if negative is followed by intracutaneous testing at 1:100,000, 1:10,000, 1:1000, and 1:100 dilutions. It has been observed on occasion the male spouse or sexual partner will have a positive skin test reaction and manifest a specific IgG and/or IgE antibody response by ELISA or western immunoblotting to one or more seminal plasma proteins.³⁷ The clinical relevance of these responses in men is currently unclear.

TREATMENT

Abstinence or the use of a condom to prevent SPP contact is an effective but not always an agreeable treatment for couples with SPH. Not being able to have unprotected intercourse places a significant amount of stress on the relationship, especially if the couple wants to conceive.

Abstinence or the use of a condom to prevent seminal plasma protein contact is an effective but not always an agreeable treatment for couples with seminal plasma hypersensitivity.

A number of different approaches have been attempted for the treatment of women with SPH. Pretreatment with oral antihistamines 30 to 60 minutes before sexual intercourse has been reported to control localized and systemic symptoms in selected cases.³⁸ Successful treatment of a woman with localized vaginal HSP hypersensitivity has also been reported using an 8% topical cromolyn sodium solution.³⁹ Nonsteroidal anti-inflammatory drugs are also effective in select patients with localized SPH, which suggests that prostanoids may be involved in some of these cases. However, none of these therapeutic approaches have been uniformly successful in the long-term treatment of women with either localized or systemic SPH.

The most effective treatment approach for women with IgE-mediated SPH has been desensitization using their sexual partner's seminal fluid proteins. Several desensitization protocols have been used with variable success.

The most effective treatment approach for women with immunoglobulin E-mediated seminal plasma hypersensitivity has been desensitization using their sexual partner's seminal fluid proteins.

Subcutaneous desensitization using whole seminal fluid was previously reported as unsuccessful. In a case report of a patient treated for 2 years using a conventional immunotherapy protocol with whole seminal fluid, the treatment was unable to induce tolerance, as the patient continued to have systemic reactions after postcoital exposure to seminal fluid.³⁴

Intravaginal desensitization using whole seminal fluid for both systemic and localized SPH reactors has been reported.^{40–45} Typically, this is accomplished by preparing log dilutions of whole seminal fluid and then beginning at a dilution of 1:10,000 or 1:100,000, intravaginally followed by instilling progressively greater concentrations of whole seminal fluid at 20-minute intervals. Although successes have been reported, especially for localized reactions, failure to prevent symptoms using this approach has also been reported. These patients who have failed intravaginal desensitization have been demonstrated to respond to treatment using the rapid desensitization protocol described below.

Rapid immunotherapy protocols have been successfully used in women with SPH, using the specific SPP fractions isolated from their partner's whole seminal plasma by Sephadex G-100 column chromatography. Those SPP eliciting a significant wheal and flare skin test reaction and/or a specific IgE antibody response by ELISA or western immunoblotting are used for desensitization.^{46–50} These protocols purposely exclude the largest-molecular-weight proteins found in fraction 1 because of their potential immunosuppressive effect, which interferes with the desired immunogenic response. This method has been successful in achieving long-lasting tolerance to SPP allergens in women with systemic and localized SPH.^{46–50} True desensitization (ie, decreased skin test threshold responses) has been obtained in several of the women treated using this treatment protocol.⁴⁷ Several investigators have reported success using this treatment approach. Ohman *et al.* reported treatment of a woman with systemic SPH for 10 months using relevant Sephadex G-100 fractionated proteins who demonstrated significant clinical improvement that directly correlated with a decline in specific IgE-SPP antibodies and a rise in specific IgG antibodies.⁵⁰

Successful treatment of women with localized SPH by rapid immunotherapy using their spouse's fractionated SPP has also been reported.⁴⁶ In a case series of 3 patients with localized SPH, all patients achieved symptomatic improvement using this approach. One of these patients treated demonstrated evidence of desensitization as she manifested a significant change in her skin test threshold response to fraction 3 postimmunotherapy. Two of these patients subsequently went on to successfully conceive children. These cases provide evidence that localized SPH involves at least in part an IgE-mediated mechanism similar to that demonstrated in women with systemic SPH.

Following desensitization, regardless of the method implemented, women must maintain constant exposure to SPP in order to maintain the

tolerogenic response by having frequent and regular sexual intercourse with their partner $2\times-3\times$ a week. This has not always been possible, because some patients or their partners may have periods apart when it is not possible to maintain this schedule. This problem has been averted by freezing pooled samples of fresh semen ejaculates, which the patient can instill using a needleless syringe intravaginally when her partner is unavailable. In addition, some patients with localized or systemic SPH have required additional booster injections of specific SPP fractions to enhance their tolerogenic responses.

CONCLUSION

Seminal plasma hypersensitivity is becoming increasingly recognized as an important women's health issue. This condition should be included in the differential diagnosis of anaphylaxis, dyspareunia, and vulvovaginitis. History, excluding other causes, including underlying STDs, and resolution of symptoms with use of a condom are very predictive in diagnosing SPH. Confirmation of this diagnosis should demonstrate a specific IgE response either to whole seminal fluid or fractionated seminal plasma proteins by skin testing and/or immunoassays prior to initiating treatment. Treatment with either graded intravaginal challenge using whole seminal fluid and/or subcutaneous immunotherapy using relevant fractionated SPP are two approaches that may provide resolution of symptoms for women with either localized or systemic SPH. Further research is required to better understand the epidemiology and immunopathogenesis of SPH. The identification of PSA as the major protein responsible for SPH should improve our ability to investigate innate and adaptive immune responses involved in the development of SPH. The ultimate objective would be to develop an effective therapy that is simpler and less costly to administer than existing treatment options.

DISCLOSURES

Potential conflict of interest: Nothing to report.

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