

Human Seminal Plasma Hypersensitivity: An Under-Recognized Women's Health Issue

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Abstract: Human seminal plasma (HSP) hypersensitivity is defined as a spectrum of systemic and/or localized symptoms after exposure to specific protein components in seminal plasma. The major antigen is believed to be prostate-specific antigen, but other proteins are likely involved in this heterogenous disorder. There are no known risk factors for developing seminal plasma hypersensitivity, although women who develop systemic symptoms are more frequently atopic. Of interest, for both systemic and localized forms, symptoms can manifest after first time intercourse in up to 50% of cases. Diagnosis requires a careful history. The gold standard for diagnosing HSP is that symptoms are completely abated with the use of a condom prophylactic. Although women with HSP hypersensitivity often have difficulty conceiving due to their inability to have unprotected sexual intercourse, infertility has not been demonstrated to be related to HSP hypersensitivity. Patients with HSP hypersensitivity often elicit positive skin prick testing and/or serum-specific immunoglobulin E to whole seminal fluid or fractionated seminal plasma proteins. Treatment involves either avoidance with the use of condoms, an 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 ≥ 1 or more of the above approaches has been very successful.

Keywords: seminal plasma hypersensitivity; dyspareunia; seminal plasma proteins; prostate-specific antigen

Introduction

Human seminal plasma (HSP) hypersensitivity was first reported by a Dutch gynecologist, J. L. H. Specken, in 1958.¹ Since then, numerous cases of HSP hypersensitivity have appeared in the literature.²⁻⁴ Human seminal plasma hypersensitivity is defined as a spectrum of systemic and/or localized symptoms after exposure to specific protein components in seminal plasma.^{1,5,6} Women with systemic HSP hypersensitivity present with symptoms of diffuse urticaria, facial, tongue, lip and throat angioedema (with or without stridor), wheezing with severe dyspnea, nausea, vomiting, diarrhea, general malaise, and in the most extreme circumstance, life-threatening hypotension, loss of consciousness, and complete circulatory failure that occurs within 30 minutes after exposure to seminal fluid.⁵ Systemic symptoms can occur with or without localized pelvic and vulvovaginal pain. Symptoms usually resolve over a 24-hour period, although urticaria, vaginal pain, and malaise may persist for several days to weeks.^{1,3,5,7,8} A previous review of HSP hypersensitivity reported 32 cases in the literature between 1958 and 1989.³ Most of these women were between the ages of 20 to 30 years and reported localized vaginal pain associated with systemic symptoms of urticaria and pruritis.³ Forty percent of these women reported symptoms the first time they had intercourse.³ Although the true prevalence of HSP hypersensitivity in the general population is unknown, a questionnaire study conducted on a group of women with suspected HSP hypersensitivity revealed that 88 (8%) of 1073 women surveyed had

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probable HSP hypersensitivity based on their symptoms and resolution of symptoms with the use of a condom.¹ If one were to extrapolate this figure to the normal population, then approximately 20 000 to 40 000 women in the United States could potentially have this condition.¹ Although avoidance of semen is an effective solution to this problem, it is not usually acceptable by women desiring to have a normal sexual relationship and/or who want to conceive.⁵⁻⁸ Therefore, HSP not only causes a serious clinical dilemma for affected women, but also leads to significant emotional strain on the interpersonal relationship with their sexual partner.¹

Clinical Presentation

The onset of HSP hypersensitivity typically begins between the ages of 20 to 30 years. Up to 30% to 40% of patients experience symptoms after first intercourse, and a common feature of both localized and systemic HSP hypersensitivity is that the use of condoms prevents symptoms in all cases.^{1,5} In our experience, localized symptoms also occur more frequently in patients than systemic reactions.^{1,5} In general, atopy is more frequent in systemic HSP hypersensitivity, but does not appear to be a risk factor for localized HSP hypersensitivity. Women with HSP hypersensitivity are not overly promiscuous, as the average number of sexual partners reported in previous questionnaire surveys is < 2.¹ Women have reported symptoms with different sexual partners, suggesting that a common seminal plasma protein (SPP) is involved in eliciting these reactions.¹ Symptom onset is rapid for both systemic and localized HSP hypersensitivity, occurring within seconds to minutes and can last several hours.¹ However, for localized reactions, vaginal discomfort can persist for several days.¹ Women with HSP hypersensitivity often present with the primary concern of whether they can conceive. To date, there are no data that connect HSP hypersensitivity with a primary infertility problem. Women are able to successfully conceive either through artificial insemination or after successful intravaginal or subcutaneous desensitization.⁹⁻¹⁴

Mechanism

There is controversy regarding which protein is the most relevant sensitizing allergen(s) for patients with HSP hypersensitivity. Investigators have reported that prostate-specific antigen (PSA), a 33–34 kD glycoprotein, is the major allergen in seminal plasma causing SPH; however, other proteins may be involved (Figure 3).^{15,16} Because of the high incidence of reactions after the first time of intercourse, many have

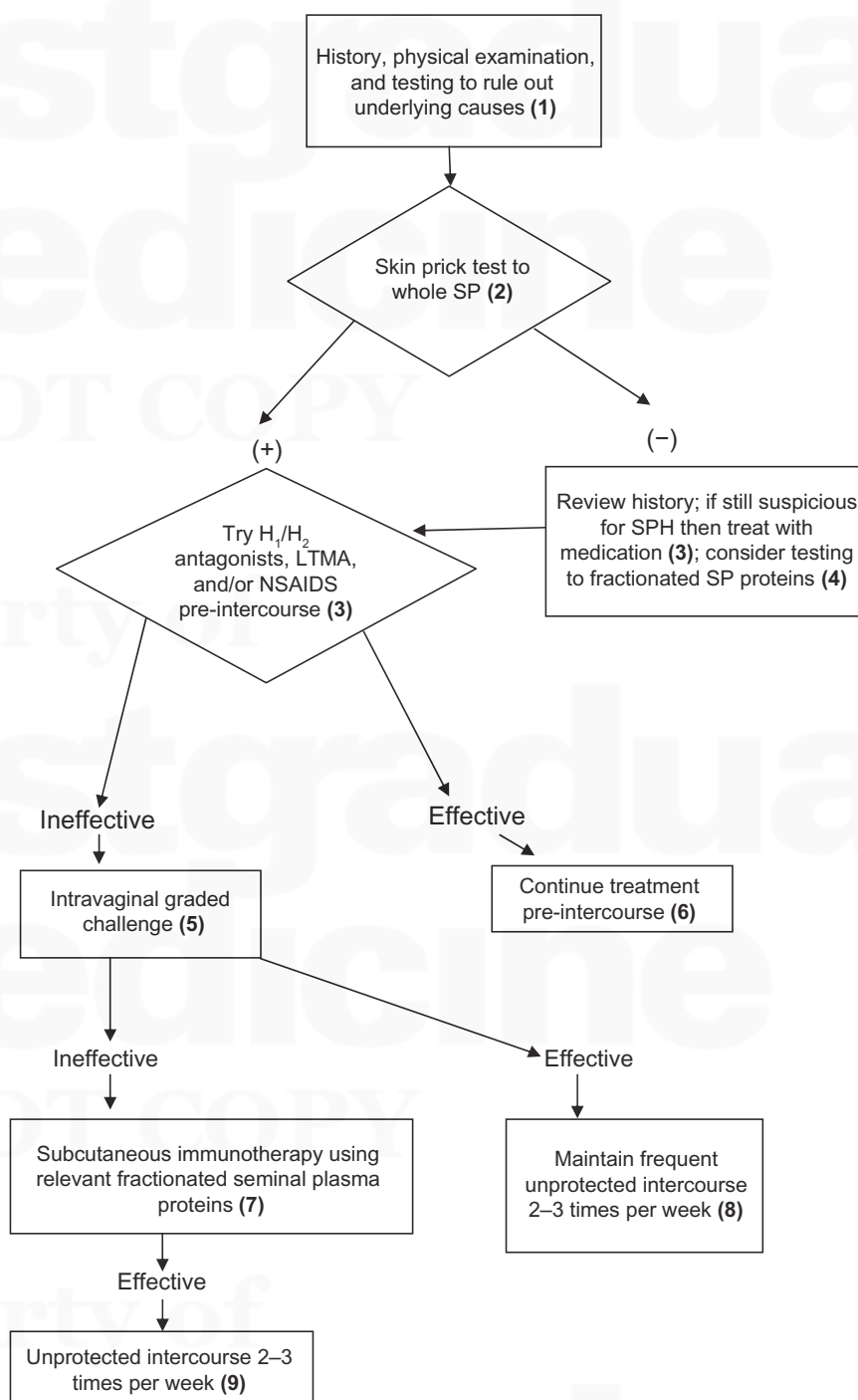
proposed a cross-reacting common protein may be involved. A recent study reported that a prostatic kallekrein protein isolated from dog epithelial extract was cross-reactive to human PSA.¹⁷ The authors speculated that this dog epithelial prostatic kallekrein likely represented a new sensitizing antigen, and that women sensitized to this antigen would be more susceptible to HSP reactions after first-time contact with human PSA from their sexual partner's semen.^{17,18} Even though women who present with HSP hypersensitivity do not always have pet dogs or are always sensitized to dog allergen, this theory requires further investigation because dog exposure can occur incidentally, and skin testing using commercial dog extracts does not exclude sensitization to PSA.

Differential Diagnosis of HSP Hypersensitivity

The diagnosis of HSP hypersensitivity is made by excluding other potential causes for systemic and localized symptoms. Other conditions that should be considered for women presenting with these symptoms include sexually transmitted diseases (STDs) (viral and/or bacterial), seasonal allergic vulvovaginitis, latex sensitivity, contact dermatitis, exercise, or vibratory-associated urticaria, transmission of food or drug protein and metabolites through body fluids to a sexual partner sensitized to these proteins or metabolites, and physical factors, such as small introitus, which could cause dyspareunia.¹⁹⁻²⁶ Women may also present with chronic vulvovaginal *Candida* hypersensitivity attributed to HSP hypersensitivity.²⁷⁻²⁹ There is 1 report of a woman reacting to other body fluids of their sexual partner, such as sweat.³⁰

Clinical Evaluation

As previously mentioned, the first step to diagnose HSP hypersensitivity is to conduct a thorough medical history (Figure 1).⁵ It is recommended that blood testing be performed on both the female and the male sexual partner to rule out underlying conditions that could manifest as HSP hypersensitivity, such as STDs. Other chronic conditions such as recurrent vulvovaginal yeast infections should be excluded by obtaining vaginal and/or cervical cultures for yeast. The work-up of a patient suspected of having HSP hypersensitivity is to first obtain a fresh ejaculate from the spouse or sexual partner, liquefy it at room temperature for 30 minutes, and then spin it down at 5000 g to separate the spermatozoa from the seminal fluid. The supernatant, which contains the seminal fluid proteins, is then removed and used to test the subject with a skin prick test. It is recommended to test the spouse or sexual partner to ensure there is no irritant

Figure 1. Human seminal plasma hypersensitivity treatment algorithm.

Abbreviations: LTMA, leukotriene-modifying agent; NSAIDs, nonsteroidal anti-inflammatory drugs; SP, seminal plasma; SPH, seminal plasma hypersensitivity.

response. If this test is negative, intracutaneous testing to whole seminal fluid is not recommended due to irritant reactions. A false-negative test can occur if the patient is taking antihistamines or due to the dilutional effect of skin prick testing using whole seminal fluid that contains numerous proteins, many of which are not relevant allergens. Com-

mercial assays are available for testing women to seminal fluid proteins, but the positive and negative predictive values of this assay are unclear. Skin prick testing to the subject's sexual partner's seminal fluid with confirmation by serologic testing to measure serum-specific immunoglobulin E (IgE) to SPPs has a high positive predictive value for

therapeutic response to SPP desensitization.^{2,7,30–35} However, in our experience, for many cases, especially localized reactors, there is often discordance between skin testing and serologic testing.

If skin and/or serologic testing is necessary, column fractionation to separate the SPPs by molecular weight is useful to isolate individual proteins for more specific prick skin testing and, if necessary, intracutaneous testing (Figure 2). This approach addresses the issue of false-negative tests due to a dilutional effect when testing is performed using whole seminal fluid. This step is also required if women are to be treated with subcutaneous immunotherapy using only the SPPs that elicit a positive skin prick or intracutaneous test. Intracutaneous testing at dilutions 1:100 000, 1:10 000, 1:1000, and 1:100 have not been found to elicit false-positive irritating reactions when the skin test responses of the female are compared with those elicited by her spouse/sexual partner.

Treatment

Various treatments for women with HSP hypersensitivity have been described. The use of prophylactic antihistamines 30 to 60 minutes before sexual intercourse has been reported to control localized and systemic symptoms in some cases.³⁶ In addition, use of a nonsteroidal anti-inflammatory drug 30 minutes before intercourse has alleviated symptoms in the woman. This suggests that prostanoids might be involved in some of these cases. Several cases of successful desensitization by intravaginal graded challenge using whole seminal fluid have been reported.^{14,37} However, in our experience, the most effective treatment approach for women with IgE-mediated HSP hypersensitivity has been immunotherapy using relevant SPPs isolated by fractionation of whole seminal fluid.^{6,38–41} Skin testing using fractionated seminal plasma proteins is performed on the patient and her

Figure 2. Fractionation of whole seminal plasma. Gel filtration chromatography shows 5 fractions designated as fractionation (Fr) I to Fr IV.⁴²

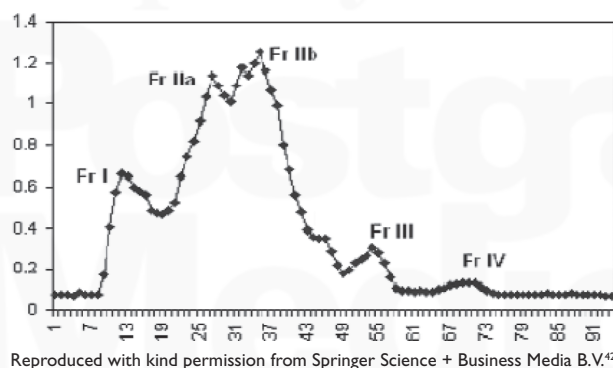
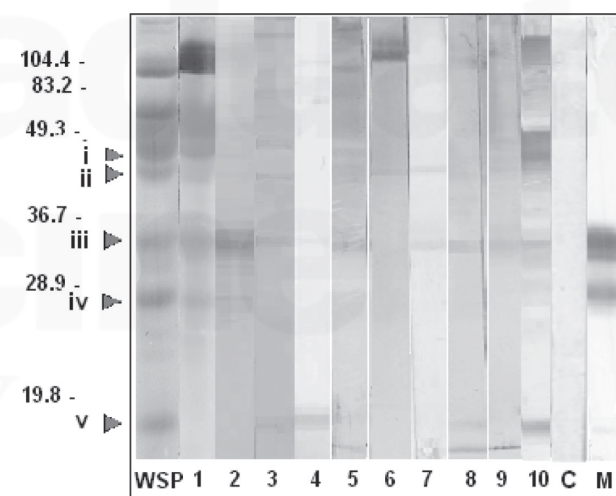


Figure 3. SDS-PAGE and IgE-specific immunoblotting of seminal plasma.⁴²



Lanes 1–10: immunoblot using 10 patients' sera. The position of the molecular weight markers are shown (kDa). Five visible bands binding to patients' IgE are marked with arrowheads.

Abbreviations: C, control; IgE, immunoglobulin E; M, immunoblotting with anti-PSA monoclonal antibody; PSA, prostate-specific antigen; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; WSP, whole seminal plasma.

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sexual partner to determine those fractionated seminal plasma proteins that elicit a specific IgE-mediated response. Rapid immunotherapy is then performed on the woman using those seminal plasma proteins that she reacted to. This treatment protocol takes approximately 3 hours. Rapid immunotherapy requires administering a series of subcutaneous injections of each SPP in the upper arm (similar to traditional allergy injections), beginning at low concentrations and building up until a total dose of 60 to 100 μ g of each protein is delivered.^{6,38–41}

Following immunotherapy, women are instructed to have unprotected natural intercourse within 24 hours. If tolerated, women must maintain their tolerance to seminal fluid proteins by having frequent and regular sexual intercourse with their partner 2 to 3 times a week.

Prognosis

Subcutaneous immunotherapy using relevant SPPs has been very successful in significantly attenuating or completely alleviating symptoms. In our experience, in properly selected patient, SPP desensitization is > 95% successful in resolving symptoms over time. Furthermore, women successfully treated have been able to conceive by natural unprotected sexual intercourse. As seminal plasma hypersensitivity has not been associated with infertility, women unable to conceive after desensitization are advised to see a fertility specialist to investigate other causes other than HSP hypersensitivity.

Summary

Human seminal plasma hypersensitivity is becoming increasingly recognized as an important women's health issue that should be considered in the differential diagnosis of not only anaphylaxis and other mast cell-releasing disorders, but also for causes of dyspareunia and vulvovaginitis. History, excluding other causes, including underlying STDs, and resolution of symptoms with use of a condom are very predictive for a diagnosis of this disorder. Demonstration of specific IgE responses either to whole seminal fluid or fractionated SPPs is necessary prior to recommending treatment with either graded intravaginal challenge using whole seminal fluid and/or subcutaneous immunotherapy using relevant fractionated SPPs. Although a favorable treatment response to intravaginal challenge using whole seminal fluid has been previously reported, reasons for it not being as effective as subcutaneous immunotherapy using relevant fractionated SPPs may be a dilutional effect from multiple irrelevant proteins and/or an inhibitory effect of T-lymphocyte responses by large molecular weight SPPs.^{6,7} The identification of PSA as the major protein responsible for seminal plasma hypersensitivity should improve our ability to understand mechanisms for this disorder and improve our ability to diagnose and treat women in the future.

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Conflict of Interest Statement

Jonathan A. Bernstein, MD discloses no conflicts of interest.

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