
Prevalence of human seminal plasma hypersensitivity among symptomatic women

Jonathan A Bernstein, MD; Rhada Sugumaran; David I Bernstein, MD; and I Leonard Bernstein, MD

Background: Experience with human seminal plasma hypersensitivity in the last decade has led to increased physician awareness of symptoms consistent with human seminal plasma sensitization in women. Incidence and prevalence of human seminal plasma hypersensitivity in women are unknown.

Objective: A questionnaire survey was distributed to determine the prevalence of human seminal plasma hypersensitivity among a population of women suspected of having this disorder.

Methods: A questionnaire designed to elicit age, symptoms, duration of symptoms, number of sexual partners, time to onset of symptoms after first human seminal plasma exposure, onset of symptoms after first intercourse, recent gynecologic procedures, history of atopy, vaginitis, food or drug allergy and family history of atopy was distributed to 1,073 women who suspected they had symptoms consistent with human seminal plasma hypersensitivity. Women were considered "possible" for human seminal plasma hypersensitivity if they reported two or more symptoms consistent with localized or systemic human seminal plasma hypersensitivity. Women were considered "probable" for disease if they fulfilled the "ultimate criterion" defined as complete prevention of symptoms with a condom. Women with "possible" localized or systemic human seminal plasma hypersensitivity who had persistent symptoms despite use of a condom served as cohort control groups.

Results: Two-hundred sixty-six women reported symptoms "possible" for human seminal plasma hypersensitivity (88 localized and 178 systemic). When the "ultimate criterion" was applied, 130 (46 localized and 84 systemic) of the 266 women were identified as having "probable" human seminal plasma hypersensitivity. The responses to most of the questions from each group were very similar. A significantly shorter time interval to symptom onset after initial human seminal plasma exposure was more common for women with "probable" localized human seminal plasma hypersensitivity compared with their cohort control group (49 months versus 108 months; $P < .02$) whereas a significantly increased number of women with "probable" systemic human seminal hypersensitivity gave positive food allergy histories compared with their cohort control group (31 versus 20; $P < .05$). Atopy did not appear to be a risk factor for human seminal plasma hypersensitivity.

Conclusions: Evaluation of women with symptoms suggestive of human seminal plasma hypersensitivity using a validated questionnaire indicates that this disorder is more common than previously recognized.

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INTRODUCTION

Human seminal plasma hypersensitivity was first reported by gynecologist,

Specken in 1958.¹ Since this index case report, numerous well documented cases of human seminal plasma hypersensitivity have been reported in the literature.^{2–8} Nevertheless, there is still concern that hypersensitivity reactions to human seminal plasma often are not readily recognized by the medical community and therefore are underreported. As a re-

sult, more accurate prevalence data on human seminal plasma hypersensitivity disorders are needed.

Presti et al previously performed an extensive literature search of human seminal plasma hypersensitivity between 1958 and 1989 and found 32 well documented cases of human seminal plasma hypersensitivity had been reported over this period of time.⁹ Most of these women were 20 to 30 years of age and had localized vaginal pain associated with systemic symptoms of urticaria and pruritus. Interestingly, 13 of 32 women experienced symptoms after the first intercourse.⁹ This review was important in establishing preliminary demographic characteristics of women presenting with human seminal plasma hypersensitivity. It also provided further insight into the clinical presentation and natural course of women with human seminal plasma hypersensitivity.

Recently, our group gathered additional information on the prevalence of human seminal plasma hypersensitivity among a suspected population of women in North America, using a validated questionnaire previously determined to have a high positive predictive value for diagnosis of human seminal plasma hypersensitivity. This questionnaire had previously been developed and used as a screening instrument during the initial evaluation of women with this disorder at our medical center. The final questionnaire diagnosis invariably correlated with confirmatory skin testing with their sexual partner's whole seminal plasma. The purpose of this survey was to determine the prevalence of localized and systemic human seminal plasma hypersensitivity disorders among a population of 1,073 women who suspected they had symptoms suggestive of this

From the University of Cincinnati College of Medicine, Department of Internal Medicine, Division of Immunology, 231 Bethesda Avenue, ML #563, Cincinnati, Ohio.

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disorder based on what they had previously learned about human seminal plasma hypersensitivity through the media or from their physicians.

METHODS

Questionnaire

A demographic and diagnostic questionnaire was used to ascertain what percentage of women in a suspected subject population had symptoms consistent with either "possible" localized or systemic human seminal plasma hypersensitivity. Prevention of reactions with use of a condom was the "ultimate criterion" by which women were given a diagnosis of "probable" human seminal hypersensitivity. The questionnaire (Appendix 1) was also designed to elicit information regarding duration of symptoms, number of sexual partners with whom they experienced reactions, onset of symptoms after the first sexual intercourse and prior temporal relationships to gynecologic procedures (ie, pregnancy, hysterectomy, or dilatation and curettage). Finally, information was obtained about each woman's atopic status and/or underlying disorders (eg, recurring vaginal candidiasis) which could mimic symptoms of human seminal plasma hypersensitivity.

Twenty-five women, evaluated at our institution for either localized or systemic human seminal plasma hypersensitivity, were originally screened and selected for treatment based on their responses to this questionnaire. Subsequent skin testing and/or vaginal challenge of these women with their sexual partner's whole seminal plasma confirmed their questionnaire diagnoses 100% of the time. These 25 women were not included in this analysis.

Criteria for Diagnostic Classification of Subject Population

Due to our interest in human seminal plasma hypersensitivity disorders, we had received more than 1,000 letters from women in North America (United States and Canada) inquiring about suspicious symptoms consistent with either localized or systemic human seminal plasma hypersensitivity. In re-

sponse to these letters we distributed a questionnaire to each of these women (Fig 1). One-thousand seventy-three questionnaires were returned and analyzed. Women were diagnosed as "possible" systemic reactors if they manifested two or more of the following symptoms: generalized pruritus, urticaria, angioedema, wheezing, chest tightness, shortness of breath, and dizziness or loss of consciousness within 30 minutes after contact with human seminal plasma. They were diagnosed as "possible" localized reactors if they manifested two or more of the following symptoms: vaginal burning, pain, swelling, and erythema or blister formation within 30 minutes after contact with human seminal plasma. Women who experienced "possible" systemic symptoms could have also experienced localized vaginal symptoms. Those women who fulfilled the criteria for either "possible" localized or systemic human seminal plasma hypersensitivity in addition to the "ultimate criterion," defined as prevention of all symptoms with the use of a condom, were classified as having either "probable" localized or systemic human seminal plasma hypersensitivity. Those women with persistent localized or systemic symptoms with use of a condom were placed in cohort control groups matched for either the "probable" localized or "probable" systemic human seminal plasma hypersensitivity reactors.

Statistical Analysis

Chi square analysis was used to analyze differences between "probable systemic" or "probable localized" groups and their respective matched cohort control groups. A $P < .05$ was considered statistically significant.

RESULTS

Of the 1,073 women who completed and returned the questionnaires, 266 (24.7%) women reported two or more symptoms consistent with "possible" localized or systemic human seminal plasma hypersensitivity. Eighty-eight women satisfied the diagnostic criteria for "possible" localized reactions and

178 women satisfied the diagnostic criteria for "possible" systemic reactions. When the "ultimate criterion" was applied, 130 (46 localized and 84 systemic) of the 1,073 women (12%) had complete resolution of their symptoms. These women were subsequently referred to as "probable" human seminal plasma reactors whereas women who had symptoms despite the use of a condom were placed in matched cohort control groups. The geographic distribution of women with "probable" localized and systemic human seminal plasma hypersensitivity correlated very well with the geographic distribution of those women placed in respective matched cohort control groups (Table 1). The homogeneous geographic distribution of these women strengthens the rationale for selecting the cohort control groups that were used for statistical comparison with women with "probable" human seminal plasma hypersensitivity.

Table 2 compares the specific questionnaire responses of women with "probable" systemic and localized human seminal plasma hypersensitivity to their respective matched cohort control groups. The distribution of women falling into "probable" localized or systemic human seminal plasma hypersensitivity groups and their respective cohort control groups based on their questionnaire responses was also very similar. In general, the panel of questions elicited similar responses from all four groups of women except for two noteworthy differences. Women categorized as having "probable" localized human seminal plasma hypersensitivity had a significantly shorter time interval from their first contact with human seminal plasma until the initial onset of symptoms compared with their cohort control group (49 months versus 108 months). This difference appeared to be due to the greater number of women with "probable" localized disease reporting symptoms after their first sexual intercourse ($P < .02$). Also of interest was the higher frequency of histories of food allergy among women with "probable" systemic human seminal

Questionnaire About Possible Allergy to Semen

1. How long have you had the problem? A. _____ months. B. _____ years.
2. Do you have the problem exclusively with your current sexual partner? A. _____ Yes B. _____ No
3. If not, how many times have you experienced a reaction with other sexual partners? _____
4. Did you have the reaction on your first intercourse? A. _____ Yes B. _____ No
5. If the answer to the above is no, how many years after your first intercourse did the first reaction occur? _____
6. Prior to the first reaction did you have:
 - A. _____ a recent pregnancy
 - B. _____ recent gynecologic operation
 - C. _____ other gynecologic problem
7. How soon after intercourse do your reactions occur?
 - A. _____ Minutes
 - B. _____ Hours
 - C. _____ Days
8. How long after intercourse do your reactions last?
 - A. _____ Minutes
 - B. _____ Hours
 - C. _____ Days
9. Do you have the following symptoms?

Generalized itching	A. _____	Yes	_____	No
Hives	B. _____	Yes	_____	No
Chest tightness	C. _____	Yes	_____	No
Shortness of breath	D. _____	Yes	_____	No
Cough	E. _____	Yes	_____	No
Wheezing	F. _____	Yes	_____	No
Dizziness	G. _____	Yes	_____	No
Faintness	H. _____	Yes	_____	No
Complete collapse (shock)	I. _____	Yes	_____	No
Unconsciousness	J. _____	Yes	_____	No
10. If your symptoms are localized only to the vaginal tissue and surrounding areas, do you have symptoms of:

Deep pain	A. _____	Yes	_____	No
Burning	B. _____	Yes	_____	No
Redness	C. _____	Yes	_____	No
Rash	D. _____	Yes	_____	No
Blisters	E. _____	Yes	_____	No
11. Does the use of condoms prevent the reaction: A. _____ Yes B. _____ No
12. How old are you now? _____
13. How old were you when the reaction first began? _____
14. Do you have other types of allergies such as asthma, hay fever, hives or eczema? A. _____ Yes B. _____ No
15. Do you have allergy to foods? A. _____ Yes B. _____ No
16. If so, which one(s)? _____
17. Do you have allergy to drugs? A. _____ Yes B. _____ No
18. If so, which one(s)? _____
19. Does anyone in your family have a history of hay fever, asthma, eczema, or hives? A. _____ Yes B. _____ No
20. Have you been treated for this condition before? A. _____ Yes B. _____ No
21. If so, what types of treatment have you had? _____
22. Have you had any prior evaluation about the possible allergic aspects of your problem? A. _____ Yes B. _____ No
23. Have you had vaginitis due to Candida? A. _____ Yes B. _____ No
24. What is the name and address of the physician who has been treating you most recently for your problem?

NAME:	_____
ADDRESS:	_____
PHONE:	_____

Figure 1. Questionnaire used in this study.

plasma hypersensitivity compared with their cohort control group ($P < .05$). Atopy did not appear to be a risk factor for developing either localized or systemic human seminal plasma hypersensitivity although the overall prevalence of atopy was greater for all four groups compared with the national estimate of 20%. There was no correlation between women with localized or systemic human seminal plasma reactions and a history for drug allergy, chronic vaginitis, or recent gynecologic procedures.

DISCUSSION

Human seminal plasma hypersensitivity has been categorized as "systemic" or "localized" disorders based on their clinical presentations.¹⁰⁻¹¹ Women with systemic human seminal plasma hypersensitivity present with symptoms of diffuse urticaria, facial, tongue, lip and throat angioedema with or without stridor, wheezing with severe dyspnea, pelvic and vulvovaginal pain, nausea, vomiting, diarrhea, general malaise and in the most extreme circumstances, hypotension, loss of consciousness and complete circulatory collapse; however, these women may also manifest symptoms experienced by localized reactors.¹⁰⁻¹³ Women with localized human seminal plasma hypersensitivity manifest symptoms localized to the vaginal area, consisting of immediate post-coital pain, burning, swelling, erythema often associated with blister formation.¹¹ Both of these diagnoses are made only after excluding other possible confounding disorders that can mimic these conditions such as seasonal vulvovaginitis, recurring vulvovaginal candidal infections, sexually transmitted diseases, and seminal plasma transfer of food allergens or drug metabolites to susceptible allergic females.¹⁴⁻¹⁸

The "ultimate criterion" for establishing a definitive diagnosis of either localized or systemic human seminal plasma hypersensitivity in this investigation was complete prevention of symptoms with the use of a condom. In the past, this diagnostic criterion cor-

Table 1. Geographic Distribution of Women with "Probable" Localized and Systemic Human Seminal Plasma Hypersensitivity Compared with Matched Cohort Control Groups

Regional Location	Localized Reactors % (n = 88)		Systemic Reactors % (n = 178)	
	Probable* (n = 46)	Controls (n = 42)	Probable* (n = 84)	Controls (n = 94)
West Mountain states	7.9	9.5	7	6.4
West Coast state†	19.5	14.3	15	13.8
Canada	2.2	4.8	2.2	2.1
Midwest states	17.4	7.1	13	19
Southeast states	26	16.7	24	22.3
Northeast states	28.3	48	39	34

* Symptoms completely prevented with the use of condoms.

† West Coast states include Alaska and Hawaii.

Table 2. Comparison of Questionnaire Responses from Women with "Probable" Localized and Systemic Human Seminal Plasma Hypersensitivity and their Matched Cohort Control Groups

Questionnaire Responses	"Probable" Localized (n = 46)	Controls Localized (n = 42)	"Probable" Systemic (n = 84)	Controls Systemic (n = 94)
Mean age, yr	24	27	23	28
Duration of symptoms, mo	106	90	91	89
Mean number of sexual partners	1.7	1.4	1.4	1.1
Mean time to onset of symptoms, mo	49	108	62	82
Onset with first time intercourse	20*	7	17	13
Previous gynecologic procedure	24	23	55	68
Chronic vaginitis	23	17	38	38
Atopy	21	16	45	56
Family history of atopy	18	24	44	61
Food allergy	17	13	31**	20
Drug allergy	13	14	39	46

* Significant correlation between localized human seminal plasma reactions and onset of symptoms after first time intercourse ($P = .01$). The relative risk by Chi Square analysis is 6.2.

** Significant correlation between systemic human seminal plasma reactions and self reported history of food allergy ($P = .03$). The relative risk by Chi Square analysis is 4.6.

related very well with confirmatory percutaneous testing of the female using their sexual partner's whole seminal plasma. Furthermore, we have had 100% success treating these women, initially diagnosed by their questionnaire responses, with immunotherapy using the fractionated seminal plasma proteins isolated from their sexual partner's whole seminal plasma.^{12,13,19} Although percutaneous skin testing tends to be specific for women with systemic reactions it has not been as reliable a marker for identifying women with localized reactions. In our experience the questionnaire is a more reliable method for establishing a diagnosis of localized human seminal

plasma hypersensitivity in women than is confirmatory percutaneous or intracutaneous testing to whole human seminal plasma.¹¹

Women who suffer with human seminal plasma hypersensitivity experience a significant amount of stress and anxiety which often leads to deterioration of interpersonal relationships because of their inability to have spontaneous unimpeded sexual intercourse. Furthermore, these reactions frequently hinder or delay couples from starting a family because of their inability to have unprotected intercourse. For these reasons, it is essential that human seminal plasma hypersensitivity reactions be recognized by obstetri-

cians/gynecologists, primary care physicians, and allergy specialists in order to minimize the duress experienced by these women and avoid unnecessary and often ineffective treatment. Additional data about the prevalence of human seminal plasma hypersensitivity would not only increase the awareness of the general medical community to this disorder but could identify potential risk factors of women who might be more susceptible to developing these reactions.

This survey identified two characteristics of women presenting with human seminal plasma hypersensitivity that provide potential clues that may eventually lead to an understanding of why certain subpopulations of women are more susceptible to human seminal plasma sensitization. First, there was an increased incidence of human seminal plasma reactions among localized reactors after their first sexual intercourse. This finding is consistent with the high frequency of cases previously reported in the literature of patients who experienced initial onset of their symptoms after first intercourse.⁹ This suggests that these women may be reacting to seminal plasma proteins that cross react with other common exogenous proteins to which they may have been sensitized previously. Second, there was a greater prevalence of self-reported food allergy among women with systemic human seminal plasma hypersensitivity. This supports the hypothesis that exposure and sensitization to seminal plasma could result from cross reactive epitopes in food proteins that are a part of the average daily American diet. Further investigation of this hypothesis is warranted.

In summary, we have used a validated questionnaire to identify the prevalence of human seminal plasma hypersensitivity reactions among symptomatic women in North America. We found that 12% of these women fulfilled the diagnostic criteria

of either "probable" localized or systemic human seminal plasma hypersensitivity. This survey indicates that human seminal plasma hypersensitivity is more common than has been reported previously. Physicians should be familiar with human seminal plasma hypersensitivity in order to expedite the proper diagnosis and evaluation of women with this disorder. The importance of diagnosing women with systemic and localized human seminal plasma hypersensitivity is highlighted by their excellent response to immunotherapy using their sexual partner's fractionated seminal plasma proteins.^{11-13,19} Work to explore the underlying immunopathogenesis of human seminal plasma hypersensitivity is ongoing. Special emphasis is being placed on localized vaginal reactions in an attempt to better understand vaginal mucosal immune responses to seminal plasma proteins.

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Jonathan A. Bernstein, MD
University of Cincinnati College of Medicine
231 Bethesda Ave., M.L.#563
Cincinnati, Ohio 45267-0563