

Is Burning Semen Syndrome a Variant Form of Seminal Plasma Hypersensitivity?

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OBJECTIVE: To identify an index population of Gulf War couples with burning semen syndrome and to determine whether burning semen syndrome was secondary to seminal plasma hypersensitivity.

METHODS: Questionnaire surveys, screening laboratory testing for underlying medical disorders, including sexually transmitted diseases and immunoglobulin G and E immunoassays specific for seminal plasma protein, were performed. If subjects met the criteria for seminal plasma hypersensitivity, the Gulf War male veteran's seminal plasma proteins were used to desensitize his female sexual partner.

RESULTS: Eighty-nine percent (188 of 211) of respondents had either personally experienced burning after contact with their own semen or had a sexual partner who had burning after contact with their semen. Asymptomatic female partners (three of five) of Gulf War veterans who exhibited specific immunoglobulin E skin and antibody responses to seminal plasma proteins responded successfully to rapid desensitization. Treatment results were confirmed by a provocative office challenge, consisting of instillation of whole seminal fluid into the female's vaginal vault and, if negative, subsequently by natural coitus.

CONCLUSION: The results of this study indicate that seminal plasma hypersensitivity may present as burning semen syndrome in a subpopulation of Gulf War couples. Proper screening of Gulf War couples with clinical features of burning semen syndrome should include assessment for seminal plasma hypersensitivity reactions, as seminal plasma protein desensitization may induce remission of burning semen syndrome. (Obstet Gynecol 2003;101:93-102. © 2003 by The American College of Obstetricians and Gynecologists.)

Since returning from the Gulf War region, some veterans and/or their female sexual partners have reported

burning, pain, and swelling of the urogenital tract after exposure to semen. This phenomenon referred to as the "burning semen syndrome" is similar to symptoms experienced by women in the general population with localized and/or systemic seminal plasma hypersensitivity.^{1,2} Women with localized seminal plasma hypersensitivity experience vaginal inflammation manifested clinically as burning and pain, which occurs within minutes after contact with their sexual partner's semen. Criteria for diagnosis of seminal plasma hypersensitivity include relief of symptoms with the use of a condom in association with the presence of specific immunoglobulin (Ig) E antibody to one or more seminal plasma protein antigens and the absence of an underlying medical disorder that could cause symptoms similar to seminal plasma hypersensitivity. Rapid desensitization using relevant homologous seminal plasma protein antigens obtained from their sexual partner's ejaculate has been effective.^{1,3,4} Response to desensitization suggests that some of these postcoital localized vaginal reactions may be IgE mediated.¹⁻³

A questionnaire survey previously distributed to 1073 women in the general population who suspected they might have symptoms consistent with localized and/or systemic seminal plasma hypersensitivity revealed that 12% fulfilled the diagnostic criteria for one or both of these disorders.⁵ This survey indicated that seminal plasma hypersensitivity reactions in women in the general population might be more common than previously recognized.⁵ However, the prevalence of seminal plasma hypersensitivity and burning semen syndrome among veterans deployed in the Gulf War theater of operations is currently unknown. The primary objective of this study was to determine whether burning semen syndrome manifested by Gulf War couples was similar or different than localized seminal plasma hypersensitivity previously reported in women in the general population.

MATERIALS AND METHODS

All subjects ($n = 211$) completed a screening questionnaire used to identify women in the general population with seminal plasma hypersensitivity. Approximately

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75% (159 of 211) of Gulf War couples with symptoms suggestive of burning semen syndrome were identified through an Internet Web page that publicized this investigation to veteran groups throughout the United States and Canada. Remaining subjects ($n = 52$) were referred for evaluation by United States Veterans hospital Gulf War physicians. However, from a total population of 211, only 67 (31.7%) could be included in this study because their symptoms were prevented with use of a condom or they did not answer this question. Of these 67 women, 43 were recruited from the Internet, and 24 were referred by Veterans hospital Gulf War physicians. A group of women in the general population ($n = 36$) who reported symptoms consistent with localized and/or systemic seminal plasma hypersensitivity was evaluated as a cohort control group in a similar manner.

Subsequently, the 67 Gulf War couples who satisfied the criterion of condom prevention or who did not answer this question were asked to complete a series of more detailed questionnaires to determine the nature of their symptoms, potential risk factors for developing burning semen syndrome as a result of exposure(s) in the Persian Gulf, and pre- and post-Gulf War medical history including post-traumatic stress disorder; 52 of 67 couples completed all questionnaires including post-traumatic stress disorder surveys.

All Gulf War and general population couples who submitted questionnaires and/or participated in the treatment phase of this study signed an informed consent approved by the University of Cincinnati Institutional Review Board and the Cincinnati Veterans Administration Medical Center.

Collection, preparation, and separation of pooled seminal plasma protein specimens were performed as previously described.³⁻⁵ Gulf War ($n = 20$) and general population ($n = 15$) men provided five pooled ejaculates collected approximately 24 hours apart and stored at 4C until shipped on wet ice. Using aseptic techniques, seminal fluid specimens were allowed to liquify at room temperature for 1 hour, and the pH was recorded. After adding an equal volume of tris-buffered saline (0.01 M of Tris-hydrochloric acid (HCl), pH 7.2, 0.14 M of sodium chloride), the mixture was vortexed thoroughly and centrifuged at $30,000 \times g$ for 1 hour at 4C using a JA-14 rotor in a Beckman J2-21M high-speed centrifuge to pellet the cells and spermatozoa. The supernatant, termed whole seminal plasma, was aliquoted and frozen at -75°C until later use.³ Ten milliliters of the donor's whole seminal plasma was fractionated on a Sephacryl S-200 High Resolution Hi-Prep 26/60 column (Amersham Pharmacia Biotech, Piscataway, NJ) in Tris saline ethylenediaminetetraacetic acid (EDTA) buffer (0.01 M of Tris-HCl, pH 7.3, 0.14 M of sodium chloride, 0.001 M

of EDTA) on a computerized fluorescent pressure liquid chromatography unit (void volume 90 mL, total column volume 320 mL). The full chromatography run was 500 mL, and 90 five-mL fractions were collected over the last 450 mL of the run. Conductivity and protein concentration (absorbance at 280 nm) were monitored continuously throughout the run. Each specimen typically yielded four to seven peaks with the largest peak eluting at and just beyond the void volume. The individual fraction peaks were pooled, concentrated ten-fold by lyophilization, and stored at -70°C until used. Protein concentrations of whole seminal plasma and fractions were determined by the bicinchoninic acid method (Pierce Chemical Co., Rockford, IL) using human IgG as a standard. All Sephacryl S-200 fraction peaks were Millipore filtered ($0.22 \mu\text{m}$) and cultured for fungal and bacterial pathogens before clinical use. Dilutions for clinical testing were made in Sterile Diluent for Allergic Extracts (Allergy Laboratories, Inc., Oklahoma City, OK).

The IgG and IgE enzyme-linked immunosorbent assays specific for whole seminal plasma obtained from the Gulf War male partner ($n = 20$) and the male partner ($n = 15$) of women from the general population with seminal plasma hypersensitivity were performed on serum from both partners of each burning semen syndrome and seminal plasma hypersensitivity couple, respectively. A 96-well polystyrene plate (Corning-Costar, Cambridge, MA, cat. no. 3590) was coated with 100 μL of aliquots of whole seminal plasma or fractions at 100 $\mu\text{g/mL}$ diluted in phosphate-buffered saline (0.01 M of phosphate buffer, pH 7.4, 0.14 M of sodium chloride) containing 0.2% sodium azide. The proteins were allowed to adsorb overnight at room temperature; then the plate was washed four times with phosphate-buffered saline containing 0.5% Tween 20. The plate was blocked in phosphate-buffered saline containing 0.5% Tween 20 + 0.5% ovalbumin (Sigma Chemical Co., St. Louis, MO) for 2 hours at room temperature. All subsequent reagent dilutions were made in phosphate-buffered saline containing 0.5% Tween 20 + 0.5% ovalbumin. Sera of each mate were diluted 1:10 and added in duplicate to the microtiter wells except for two Gulf War men who did not have a female sexual partner at the time of this study. One symptomatic and five asymptomatic control sera were run in duplicate on whole seminal plasma and fractions for each couple. After incubation for 1 hour at room temperature, the plate was washed four times in phosphate-buffered saline containing 0.5% Tween 20, and 100 μL of a 1:10,000 dilution of alkaline phosphatase conjugated goat antihuman IgG (Sigma, Cat. No. A-3187) was added to each well. After incubation for 1 hour at room temperature, the plate was again washed

four times, and 100 μ L of 1 mg/mL of p-nitrophenyl phosphate substrate in diethanolamine buffer was added to each well, and the color development was stopped with 100 μ L of 1N sodium hydroxide after 30 minutes. The optical density was read at 405 nm, and means of duplicate wells were calculated.

For IgE antibody detection, an indirect assay was employed. The plates were coated, blocked, and incubated with serum as above for IgG. After washing, 100 μ L of 1:1000 dilution of goat antihuman IgE (Sigma, Cat. No. I-0632) was added to the wells, and incubated at room temperature for 1 hour. After washing, 100 μ L of a 1:1000 dilution of alkaline phosphatase conjugated rabbit antigoat IgG (cat. no. 15-13-06; Kirkegaard and Perry, Gaithersburg, MD) was added and incubated for 1 hour at room temperature. The plate was washed, substrate added, and read as above. A positive IgG or IgE antibody response was defined as greater than the mean optical density plus three standard deviations of five asymptomatic control sera. An optical density greater than 0.2 was considered a positive response.

Couples were selected for the treatment phase of this project if: 1) their symptoms were completely eliminated with use of a condom, 2) they had normal screening blood/culture tests, and 3) they had elevated specific IgE antibodies and/or positive cutaneous responses to whole seminal plasma. Five Gulf War and two general population cohort control couples who satisfied these qualifying criteria consented to participate in the treatment phase.

Specifically, all male participants in the treatment phase were screened by blood and culture tests to exclude chronic medical disorders (ie, diabetes mellitus, prostatitis) that could be responsible for their symptoms. All women ($n = 7$) had a pelvic examination, which included a Papanicolaou smear and vaginal and cervical cultures to exclude active viral, bacterial, or fungal/yeast infections.

All volunteers received percutaneous (prick/puncture) testing to common seasonal and perennial allergens, which included box elder (tree), fescue (grass), short ragweed, *Alternaria*, *Aspergillus* (representative molds), cat, and dust mite along with positive (histamine 10 mg/mL) and negative (saline) controls to assess for a preexistent atopic status.

Percutaneous testing to whole seminal plasma and each chromatographic seminal plasma protein fraction from the male partner was performed on both the male and female partner from each treatment couple. Intracutaneous testing beginning at a 10^{-6} (volume per volume) concentration using each major chromatographic fraction was performed by placing sequentially log-fold higher concentrations up to a final concentration of 10^{-1} (volume per volume). A positive skin test was defined as

greater than or equal to 3 mm wheal with erythema, compared with a negative saline control. Histamine-HCl (1 mg/mL) was used as a positive control for intracutaneous tests.

Women with positive skin or specific IgE tests were desensitized using relevant seminal plasma protein fractions. Seminal plasma protein fraction 1 was excluded because this large molecular weight protein fraction had been previously demonstrated to interfere with successful desensitization.^{3,4} The initial concentration chosen for desensitization was two log-fold lower than the skin test concentration or in vitro IgE antibody response that elicited a positive response. All injections were administered subcutaneously in the deltoid region of the upper arms by doubling concentrations every 10 minutes. A maximum of 100 μ g of protein was administered for each fraction.

Twenty-four hours postdesensitization, women were skin tested again to those fractions that initially elicited a positive reaction(s) to determine if there was a post-treatment shift in threshold skin test response. Under controlled conditions in an office setting, a fresh ejaculate sample (volumes ranging between 1.5–3 mL) obtained from the male partner was instilled into the female's posterior vaginal vault. The presence or absence of symptoms was monitored over the next 2 hours. If symptoms were not observed, the couple was instructed to have unprotected intercourse within the next 24 hours. A successful treatment response was defined as lack of symptoms after both laboratory challenge and unprotected coitus. Women who responded to treatment were encouraged to engage in regular unprotected intercourse with their partners at least two to three times a week to maintain seminal plasma protein tolerance.

The χ^2 analysis or Fisher exact test was used to analyze all categorical data, and the Student t test was used to analyze continuous data. An α level of .05 was used for all statistical tests.

RESULTS

A total of 211 Gulf War male veterans from 41 states, Puerto Rico, Canada, and the United Kingdom who made initial inquiries through the Web site or by phone about the purpose of this study completed a screening questionnaire used to evaluate women with seminal plasma hypersensitivity in the general population. Eighty-nine percent (188 of 211) of these respondents had either personally experienced burning after contact with their own semen or had a sexual partner who experienced burning after contact with their semen. Only 7% (15 of 211) reported having these symptoms before their Gulf War experience, whereas 48% (101 of

211) developed symptoms immediately after the first sexual contact upon returning home. Less than 50% (97 of 211) of Gulf War couples experienced relief of symptoms with use of a condom compared with 100% relief that has been typically reported by general population couples with seminal plasma hypersensitivity. Surprisingly, only 42% (89 of 211) of Gulf War couples had sought medical attention for these symptoms before this survey.

Thirty-two percent (67 of 211) of the Gulf War population who satisfied preliminary entry criteria (complete relief of symptoms with use of a condom or nonusage of condoms) were asked to complete more comprehensive questionnaires about seminal plasma hypersensitivity, burning semen syndrome, and post-traumatic stress disorder. Seventy-eight percent (52 of 67) of this population completed both the more extensive questionnaires and the post-traumatic stress disorder surveys. There were no Gulf War female respondents.

Table 1 compares characteristics of the Gulf War veterans' female partners ($n = 67$), who were experiencing localized or systemic burning semen syndrome symptoms, with a cohort population of women in the general population ($n = 36$) experiencing either localized or systemic seminal plasma hypersensitivity reactions. Women in the general population with localized seminal plasma hypersensitivity reactions were more likely to have a personal history of atopy compared with the Gulf War veterans' female sexual partners experiencing localized vaginal symptoms ($P < .05$). Women in the general population with localized and/or systemic plasma hypersensitivity symptoms also reported a family history of atopy more frequently than the female sexual partners of Gulf War veterans ($P < .05$).

Further analysis of the more detailed questionnaire responses revealed that only 40% (27 of 67) of the Gulf War veterans' female partners actually met the absolute criterion for diagnosis of seminal plasma hypersensitivity (ie, complete relief of symptoms with the use of a condom) compared with 75% of general population women with symptoms suggesting seminal plasma hypersensitivity (27 of 36) ($P < .05$). Many of the Gulf War and general population subjects had never used condoms or used them incorrectly, thereby resulting in symptoms. Such information could not be ascertained in the original screening questionnaire, thereby necessitating completion of more extensive questionnaires in these uncertain subjects. There were no differences between Gulf War and general population groups with respect to age, nature, or duration of symptoms experienced, number of sexual partners, or other predisposing conditions that have been previously associated with seminal plasma hypersensitivity reactions.^{1,3,6}

Table 2 summarizes responses to a spectrum of questions answered by Gulf War couples ($n = 52$) who completed the more extensive questionnaires and post-traumatic stress disorder surveys. These Gulf War couples were divided into "healthy" ($n = 14$) or "unhealthy" ($n = 38$) groups based on their responses. An "unhealthy" status denoted the presence of multiple somatic symptoms consistent with "Gulf War syndrome," whereas a "healthy" status was defined as having no physical complaints other than burning semen syndrome symptoms. The "healthy" Gulf War men with isolated burning semen syndrome (14 of 52) were younger ($P < .03$) and less likely to report involvement in decontamination operations ($P < .05$). The "healthy" group was also less likely to experience symptoms after direct exposure to their own semen compared with their "unhealthy" counterparts ($P < .02$). Of additional interest was the fact that the "unhealthy" Gulf War male group was more likely to be undergoing treatment for post-traumatic stress disorder compared with their "healthy" counterparts ($P < .02$). A "healthy" or "unhealthy" status did not distinguish the occurrence of burning semen syndrome in the female partners.

Serum specimens and suitable pooled ejaculates for whole seminal plasma specific IgG and IgE antibody levels were obtained from 20 Gulf War and 15 general population couples who had completed all questionnaire surveys. Table 3 summarizes the specific IgG and IgE responses to whole seminal plasma for these subjects. A positive response was defined as greater than the mean optical density of five asymptomatic whole seminal plasma control sera + three standard deviations (greater than 0.2). In general, specific IgG and IgE responses were larger for both Gulf War and general population female sexual partners compared with their male counterparts. However, there was no statistical difference in antibody responses between the Gulf War and general population men or between their female sexual partners. The general population women had statistically significant greater specific IgE responses to whole seminal plasma compared with their male partners. Interestingly, several Gulf War and general population men exhibited increased IgG antibody responses to their own whole seminal plasma. One Gulf War man had elevated specific IgE antibody to autologous whole seminal plasma. None of the general population men showed specific IgE antibody responses to their own whole seminal plasma.

Five Gulf War burning semen syndrome and two general population couples with localized seminal plasma hypersensitivity reactions who volunteered for more extensive laboratory screening were selected for the subsequent treatment protocol based on the severity of their symptoms and availability for clinical investiga-

Table 1. Comparison by Subtype of Gulf War Female Partners With Burning Semen Syndrome With Civilian Women With Seminal Plasma Hypersensitivity*

Item	Gulf War female partners with systemic symptoms (n = 28)	General population women with systemic symptoms (n = 19)	Gulf War female partners with localized symptoms (n = 39)	General population women with localized symptoms (n = 17)
Age of onset (y)				
<30	21	13	25	14
>31	7	6	14	3
Race (white)	27	18	39	17
Reactions				
Urticaria/pruritus	25	16	17 [†]	7 [†]
Chest tightness/dyspnea/cough/whizzing	19	16		
Dizziness/faintness	21	13		
Complete collapse/unconscious	2	5		
Local pain/burning	24	12	36	17
Redness/rash/blisters	23	12	29	15
Onset of symptoms (min)				
0-60	24	18	34	16
>60	4	1	5	1
Duration of symptoms (h)				
<24	10	5	21	12
>24	18	14	18	5
Prevented by condom				
Yes	10	14	17	13
Never tried or used condom incorrectly	18	5	22	4
Atopy				
Yes	15	13	11 [‡]	10 [‡]
No	13	5	28 [‡]	5 [‡]
Unknown	0	1	0 [‡]	2 [‡]
Multiple partners				
Yes	4	6	3	2
No	23	13	35	15
Unknown	1	0	1	0
Predisposing conditions				
First intercourse	12	5	12	8
History of pregnancy, gynecologic/urologic surgery	8	6	8	4
Family history of atopy				
Yes	10 [‡]	13 [‡]	12 [‡]	12 [‡]
No	17 [‡]	5 [‡]	27 [‡]	5 [‡]
Unknown	1 [‡]	1 [‡]	0 [‡]	0 [‡]
Diagnosis of seminal plasma hypersensitivity				
Probable	10	14	14	12
Possible	9	3	9	4
Undetermined	9	2	16	1

* χ^2 or Fisher exact analysis excluding "unknown" responses.

[†] Women identifying only pruritus as a systemic symptom were classified as localized responders.

[‡] $P < .05$.

tion at our facility. No abnormal tests were found in these 14 volunteers. Several other Gulf War couples were excluded from the treatment phase of this project because of abnormal laboratory tests. For example, three Gulf War veterans' female sexual partners had significant antinuclear antibody titers (greater than 1:160), and

four had positive cervical cultures for yeast, *Streptococcus*, or *Ureaplasma urealyticum*, a strain of *Mycoplasma*. One woman had a significantly elevated sedimentation rate (Westergren sedimentation rate 68) in association with an active *Mycoplasma* infection. Interestingly, subsequent 4-week treatment courses of doxycycline in this woman

Table 2. Summary of “Healthy” and “Unhealthy” Gulf War Veterans’ Responses to Extended Questionnaire and Posttraumatic Stress Disorder Surveys

Responses	Healthy (<i>n</i> = 14)	Unhealthy (<i>n</i> = 38)	<i>P</i>
Average age (y)	32	36	<.03*
Average length of tour (mo)	5.2	5.8	.35
Reported chemical exposures	32	32	.18
Diagnosis/treatment of Leishmaniasis	0	19	>.999
Uranium exposure	14	14	.75
Exposure to biologic agents	12	26	.33
Ingestion of pyridostigmine bromide	11	26	.73
Side effects from pyridostigmine bromide	5	22	.34
Exposure to pesticides	5	23	.13
Received vaccinations	8	24	.75
Previous evaluation for post-traumatic stress disorder	1	24	<.001
Previous treatment for post-traumatic stress disorder [†]	1	14	<.05
Respondents probable for post-traumatic stress disorder [‡]	1	16	.02
Involvement in decontamination operations	1	15	<.05
Current state of health	11 good or better	0 good or better	<.001
Sexually transmitted disease	1	6	.66
Reaction to semen	3	24	<.02
Sexual partner has localized/systemic reaction	14	33	.31
Sexual partner has systemic reaction only	6	15	>.999
Onset of reaction with first sexual encounter after returning from Gulf War	3	11	.73
Condoms eliminate reaction	5	20	.36
History of vasectomy	2	9	.71
History of fertility problems	1	5	>.999
History of allergies (hay fever, asthma)	1	12	.15
Food allergies	0	7	.17
Drug allergies	1	10	.25
Same sexual partner before and after Gulf War	6	20	.76

Unhealthy = multiple somatic symptoms suggestive of Gulf War syndrome; Healthy = no other physical complaints.

* Analyzed by Student *t* test; all other values analyzed using Fisher exact test.

[†] Based on self-reported history.

[‡] Based on completion of Mississippi Post-Traumatic Stress Disorder Rating Scale (*n* = 44).

and two others with positive ureaplasma cervical cultures did not relieve their urogenital symptoms after contact with semen. This lack of response was consistent with their *Mycoplasma* genomic deoxyribonucleic acid analyses (International Molecular Diagnostics, Huntington Beach, CA), which was negative in all of these subjects.

Table 4 summarizes the characteristics of all the women who participated in the treatment phase of this study. This includes symptoms manifested by all female partners, their skin test responses before and after rapid desensitization to relevant homologous seminal plasma proteins, specific IgG and IgE responses to seminal plasma proteins fractions, and clinical responses to rapid desensitization. Only Gulf War couples from the “healthy” status group (Table 2) were selected for seminal plasma protein rapid desensitization to eliminate any potential confounding variables of an “unhealthy” status, which might confuse the treatment response. None of the Gulf War or general population men exhibited

burning semen syndrome in response to their own semen. All of the Gulf War female partners and women from the general population partners exhibited localized vaginal symptoms after contact with semen except for the women of Gulf War couple 4 and general population couple 1, who had diffuse hives in addition to localized vaginal burning and pain after seminal fluid contact.

Positive skin test responses to seminal plasma protein fraction 5 and/or 6 at a concentration of less than or equal to 10^{-1} (volume per volume) were present in all Gulf War veterans’ female partners. Specific serologic IgE responses to seminal plasma protein fractions were identified in three of the five women. Total agreement between skin test and specific seminal plasma protein fraction antibody responses was not observed in any of the Gulf War female partners. In the woman of general population couple 1, there was good correlation between specific seminal plasma protein skin test and IgE antibody responses. Cutaneous responses to seminal plasma protein fractions were elicited in the woman of general

Table 3. Whole Seminal Plasma-Specific Immunoglobulins G and E Optical Density Values in Gulf War and General Population Men and Women With Statistical Comparison Between Groups

	Gulf War couples (n = 20)				General population couples (n = 15)			
	IgG		IgE		IgG		IgE	
	Male	Female	Male	Female	Male	Female	Male	Female
Mean OD	0.15	0.4	0.12	0.37	0.15	0.37	0.11*	0.55*
Mean SD	0.15	0.73	0.08	0.81	0.18	0.45	0.1	0.83
Mean SEM	0.03	0.16	0.02	0.18	0.05	0.12	0.03	0.21
	GW IgG male vs female	GW IgE male vs female	General population IgG male vs female	General population IgE male vs female	GW IgG vs general population IgG male	GW IgE vs general population IgE male	GW IgG vs general population IgG female	GW IgE vs general population IgE female
P	.14	.18	.09	.05*	.88	.73	.91	.51

IgG = immunoglobulin G; IgE = immunoglobulin E; OD = optical density; SD = standard deviation; SEM = standard error of the mean; GW = Gulf War.

An OD + three SD values > 0.20 was considered significant based on five asymptomatic control sera.

*Statistically significant differences using the Student *t* test.

population couple 2 only at a full strength or 10^{-1} (volume per volume) concentration, and no specific IgE antibody responses to seminal plasma protein fractions were detected. Previous experiences in the evaluation of women in the general population with seminal plasma hypersensitivity indicate that there is often a lack of correlation between specific seminal plasma protein skin tests and serologic IgE antibody responses.¹ This observation is most likely attributed to the majority of seminal plasma protein-specific IgE antibody being bound to tissue mast cells and basophils, resulting in very low

levels of unbound specific IgE available for detection in the serum. Therefore, as a rule, selection of seminal plasma protein fractions suitable for rapid desensitization is based predominantly on skin test responses.

Skin test results in the men revealed that three of four Gulf War men who could be tested (one had dermatographism with serologic evidence of specific IgE) had positive skin tests to seminal plasma protein (greater than or equal to 10^{-1} volume per volume) fractions, whereas neither of the general population men demonstrated similar reactivity.

Table 4. Treatment Outcomes for Female Partners of Gulf War and General Population Couples Diagnosed With Seminal Plasma Hypersensitivity

Couple	Symptoms	Pretreatment skin tests to fractions (v/v)	Posttreatment skin tests to fractions (v/v)	Specific IgG to fractions	Specific IgE to fractions	Treatment response to relevant fractions
Gulf War Couple 1	Local	5 (10^{-3}) 6 (10^{-2})	5 (10^{-1}) 6 (10^{-2})	3, 4, 5	3, 4	Successful (Fxs 3, 4, 5)
Gulf War Couple 2	Local	5 (10^{-2}) 6 (10^{-3})	5 (10^{-3}) 6 (10^{-2})			Partially successful* (Fxs 5, 6)
Gulf War Couple 3	Local	5 (10^{-1}) 6 (10^{-3})	ND			Not successful (Fxs 5, 6)
Gulf War Couple 4	Systemic	5 (10^{-3}) 6 (10^{-3})	5 (10^{-2}) 6 (10^{-2})	3, 4, 5	4	Successful (Fxs 5, 6)
Gulf War Couple 5	Local	5 (10^{-2})	5 (10^{-1})	5	4	Successful (Fx 5)
General population Couple 1	Systemic	2a (10^{-1}) 3 (10^{-2}) 4 (10^{-1})	2a (10^{-1}) 3 (10^{-2}) 4 (10^{-1})	4	2a, 3	Successful (Fxs 2a, 3, 4)
General population Couple 2	Local	2b (FS) 3 (10^{-1}) 4 (FS)	ND			Not successful (Fxs 2b, 3, 4)

v/v = volume per volume; Fxs = fractions; ND = not done; FS = full strength.

*Milder symptoms after seminal fluid contact.

The female partners of Gulf War couples 1, 4, and 5 had complete relief of their symptoms after rapid desensitization using the seminal plasma protein fractions that elicited positive skin test responses. Similarly, the woman of general population couple 1 also responded successfully to rapid desensitization using those seminal plasma protein fractions that gave a positive cutaneous response. Specific seminal plasma protein IgE antibodies were detected in all women who were successfully treated. The female partner from Gulf War couple 2 with no specific seminal plasma protein IgE antibody had a partial response to treatment in that her symptoms were milder after subsequent exposure to semen. The woman from Gulf War couple 3 with lack of response did not show specific IgE to seminal plasma proteins. Similarly, the woman from general population couple 2 cited above, with equivocal skin tests and no specific IgE antibody to seminal plasma protein, did not improve after therapy.

Skin testing to relevant seminal plasma protein fractions in women postdesensitization revealed significant log-shift threshold changes in the three Gulf War female partners who responded to treatment (Table 4). This shift in skin test threshold response was of a similar magnitude to that previously reported in women with localized seminal plasma hypersensitivity treated successfully with seminal plasma protein rapid desensitization.^{1,2}

Those women who improved after desensitization were instructed to have routine sexual intercourse (two to three times per week) to maintain "tolerance." One-year follow-up of the successfully treated cases revealed that their urogenital burning semen syndrome or localized seminal plasma hypersensitivity symptoms had not recurred.

DISCUSSION

Health care problems experienced by veterans who participated in the Persian Gulf War have been a serious concern to the United States Armed Forces and veteran advocacy groups. Considerable funding has been allocated to investigate causation and treatment for these health-related problems. Unfortunately, overall evaluation of several funded epidemiologic studies by expert panels reached a consensus that illnesses of Persian Gulf War veterans resulted from various causes and could not be explained by a common denominator.⁷ However, one advisory panel noted that rare or mild illnesses could be missed by a large clinical survey such as the Persian Gulf War registry, which has been used to examine approximately 10% of all United States Gulf War veterans.⁸ Burning semen syndrome is an example of such a

rare but well-documented disorder that surfaced after the conclusion of the Persian Gulf War. Evaluation of this condition has been hindered for many of the same reasons that have prevented a better understanding of other Gulf War-related illness. These include but are not limited to: 1) poor case definition of the underlying problem, 2) multiple concomitant somatic and psychologic complaints that obfuscate a focused evaluation, and 3) logistical difficulties in evaluating these individuals over time.⁹⁻¹¹

This project was initiated to determine whether the burning semen syndrome disorder was similar to localized seminal plasma hypersensitivity that occurs in women from the general population. The initial phase of this study was to identify Gulf War veterans with burning semen syndrome and to determine potential risk factors for this problem. Preliminary clinical evaluation was undertaken in Gulf War veterans and their mates whose histories of burning semen syndrome were consistent with seminal plasma hypersensitivity. This involved laboratory testing to exclude underlying causes masquerading as burning semen syndrome or seminal plasma hypersensitivity and measurement of specific IgG and IgE antibodies to whole seminal plasma. From this population, eligible Gulf War couples were selected to determine whether rapid desensitization to homologous seminal plasma protein would be an effective intervention strategy. A population of general population subjects with seminal plasma hypersensitivity was evaluated concomitantly, and two couples from this group were selected for cohort comparison of treatment efficacy.

There are several inherent limitations to this study. First, this population-based survey depended on identifying a representative portion of Gulf War couples with burning semen syndrome. This approach typically results in a population selection bias because usually only well-motivated individuals volunteer to participate. Second, the restraints of the protocol made it difficult, if not impossible, to evaluate couples at remote sites. Often, couples did not have access to a primary care physician or a local/regional veterans hospital. Third, as the study progressed, the enthusiasm of many couples diminished. Although statistical analysis could be performed on the questionnaire respondents, the small size of the treated population permitted only descriptive data. Identification of a cohort, control population was susceptible to the same limitations that were encountered for identifying the Gulf War population. To minimize demographic bias, the same inclusion/exclusion criteria were precisely the same for both the Gulf War and general population couples. All questionnaires were designed to ensure that

valid information was obtained by asking questions in different ways to confirm reliable responses.

The common denominator of Gulf War burning semen syndrome and seminal plasma hypersensitivity in the general population are the symptoms of localized vaginal burning and pain immediately after contact with semen.¹² However, the initial questionnaire survey and subsequent clinical evaluation revealed cogent differences. In seminal plasma hypersensitivity occurring in the general population, the man is typically asymptomatic, and skin test responses to homologous semen are negative. Symptoms experienced by women invariably disappear after use of a condom.^{1,6} In contrast, male partners in the Gulf War burning semen syndrome often complain of burning after contact with their own ejaculates, and several of the men in this study also exhibited positive skin tests to their own seminal plasma proteins. Moreover, less than half of the Gulf War female partners experienced relief of symptoms if partners used condoms correctly. The questionnaire survey revealed that many Gulf War couples with burning semen syndrome exhibited other features of the Gulf War syndrome, which tended to complicate the clinical evaluation and ultimate diagnosis of burning semen syndrome. When Gulf War veterans were divided into "healthy" and "unhealthy" groups, a significant correlation between post-traumatic stress disorder and the "unhealthy" group was established. For this reason, Gulf War veterans who did not have irrelevant concomitant somatic/psychologic complaints and their sexual partners were preferentially selected for the treatment phase of this project to evaluate responses to therapy exclusive of these possible confounders.

In general, both women from the general population and female partners of Gulf War veterans exhibited specific IgG and IgE antibody responses to whole seminal plasma.¹³ However, as previously reported, the results of this study demonstrated that IgE-mediated skin testing, with or without confirmatory in vitro specific IgE antibody responses, was the best predictor of successful outcome after seminal plasma protein desensitization in either the general population or Gulf War female partners.¹ The combination of specific IgE skin tests to seminal plasma protein and successful therapeutic responses to rapid desensitization in three of these Gulf War couples indicates that burning semen syndrome is induced by an IgE-mediated mechanism in a subpopulation of Gulf War couples presenting with this problem. The cause(s) of non-IgE mediated burning semen syndrome remains to be determined.

Several Gulf War and male subjects from the general population were noted to also produce low levels of specific IgG and IgE antibody to their own seminal

plasma protein. Indeed, three of four Gulf War men also demonstrated IgE-mediated skin test reactivity. The significance of these findings is unknown but could represent either exogenous cross-reactivity between common environmental proteins or immunologic mimicry resulting in autoantibodies to one or more seminal plasma protein antigenic determinants in men. One or both of these possibilities is suggested by the fact that the vast majority of patients claiming to have burning semen syndrome by history did not have these symptoms before the Gulf War exposure. Further work is necessary to determine whether antibody responses in male subjects have a functional role in the underlying immunologic phenomena associated with seminal plasma hypersensitivity and burning semen syndrome.

In summary, the results of this study revealed that couples from the general population with seminal plasma hypersensitivity and Gulf War couples with burning semen syndrome have similar overlapping features. The precise causes and triggers for seminal plasma hypersensitivity in general population couples and for burning semen syndrome in Gulf War couples remain unknown. However, more detailed assessment of a Gulf War population with burning semen syndrome in this investigation not only identified a subgroup of couples with seminal plasma hypersensitivity but also suggested a basis for successful treatment. For this reason, it is important to institute an evaluation for seminal plasma hypersensitivity in Gulf War couples presenting with burning semen syndrome, and skin tests to homologous seminal plasma protein is an essential component of such a workup. The results clearly demonstrated that a new case definition of some Gulf War patients with burning semen syndrome should include seminal plasma hypersensitivity.

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