Hormonal And Seminal Plasma Hypersensitivity

Jonathan A. Bernstein, M.D.
Professor of Medicine
Department of Internal Medicine
Division of Immunology/Allergy Section

department of Internal Medicine

UNIVERSITY OF Cincinnati

Objectives

At the end of this lecture the participant will be able to:

- Define seminal plasma hypersensitivity and discuss treatment and management in the Allergist's office
- Discuss candida vulvovaginal hypersensitivity and treatment
- Discuss the evaluation, diagnosis and treatment of women presenting with progestin hypersensitivity

Case Study 1

- 37 year old female married for 8 years presented with:
- Localized vaginal burning and pain after contact with seminal fluid which began immediately after her first pregnancy
- Symptoms progressed to bronchospasm with cough
- Subsequently developed more severe systemic symptoms consisting of diffuse itching, wheezing, shortness of breath, flushing, facial swelling and hives
- On three occasions she experienced loss of consciousness with convulsions that occurred within 30 minutes after unprotected sexual intercourse
- After the 3rd event, the association between these episodes and unprotected sexual intercourse was finally established

Past Medical History

- No history of drug allergies
- History of food allergy to red and green peppers (nausea and vomiting with headache)
- No sexually transmitted diseases
- One child G1P1Ab0
- History of seasonal allergic rhinitis and cat allergy
- Was told she had asthma but never physician diagnosed; had no medication
- Husband with a food allergy to mushrooms but otherwise very healthy

Differential Diagnosis

- Seminal plasma hypersensitivity
- Seasonal allergic vulvovaginitis
- Recurrent allergic Candida vulvovaginitis
- Seminal plasma fluid transfer of a drug or drug metabolite to a drug-sensitive female
- Seminal plasma transfer of food allergens to a food allergic female
- Infection (Chronic yeast, STDs)
- Contact dermatitis
- Structural problems
- Physically induced symptoms (exercise or vibratory angioedema)

Bernstein JA, et.al. Seminal Plasma Hypersensitivity. Eds. Amin S, Lahti A, Maibach HI IN: Contact Urticaria Syndrome. New York, CRC Press 1997, pp.241-259.

Seminal Plasma Hypersensitivity
Definitions

- ***Systemic:*** Symptoms of diffuse urticaria, facial, tongue, lip and throat angioedema with and without stridor, wheezing, diarrhea and in the most extreme situations vascular collapse
- ***Localized:*** Immediate post-coital vulvovaginal burning and pain which may persist for hours or days
- May have overlap – Systemic and Localized symptoms

For both types, symptoms alleviated with use of a condom

Bernstein JA, et.al. Ann Allergy Asthma Immunol 1997; 78:54-58.

Seminal Plasma Hypersensitivity
Prevalence

- Unknown
- Estimated 20-40,000 women with this condition
  - Based on responses from a Phil Donahue show which had an estimated 446,000 viewers/show (CNN.com)
  - 1,073 letters received (.24% response); 130 (.03%) had probable SPH based on complete resolution of symptoms with use of a condum
  - Extrapolated to 100 million sexually active women in US (29,000 women)

Bernstein JA, et.al. Ann Allergy Asthma Immunol 1997; 78:54-58.

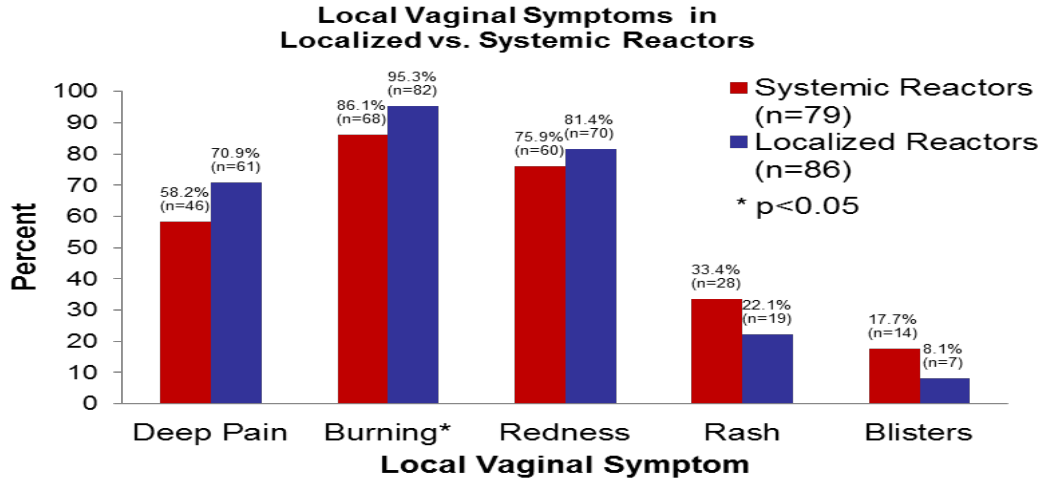
Comparison Between Localized And Systemic HSP

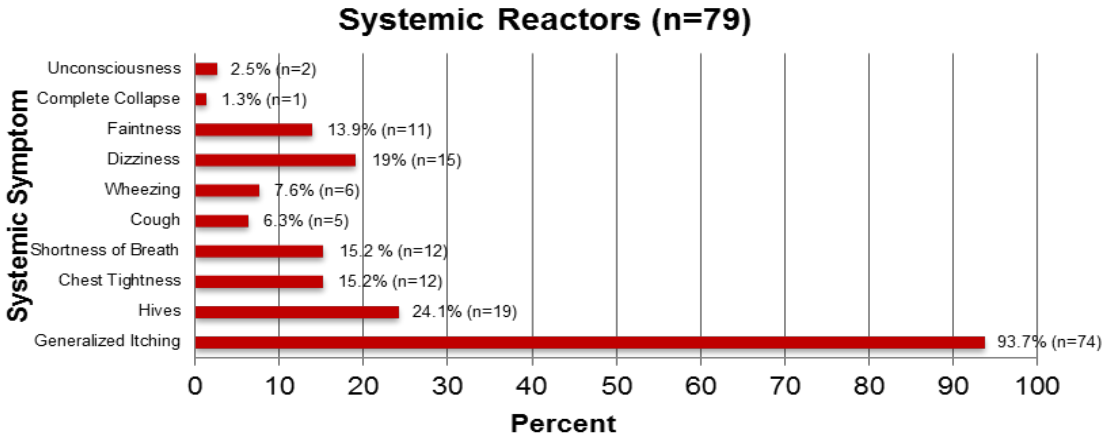
Questionnaire responses	Localized (n=46)	Systemic (n=84)
Mean age (yrs)	24	23
Duration of symptoms, mo	106	91
Mean # sexual partners	1.7	1.4
Mean time to onset of symptoms, mo	49	62
Onset with first time intercourse	20	17 (p<.02)
Previous gynecologic procedures	24	55
Chronic vaginitis	23	38
Atopy	21	45
Family history of atopy	18	44
Food allergy	17	31 (p<.05)
Drug allergy	13	39

Bernstein JA, et.al. Ann Allergy Asthma Immunol 1997; 78:54-8.

Questionnaire Responses	Systemic Reactors (n=79)	Localized Reactors (n=86)	p-value
Mean age, yrs	29.2	26.4	0.01
Duration of Symptoms, mos	58	40.8	0.03
Symptoms with First Sexual Intercourse	40 (50.6%)	33 (38.4%)	0.11
Time after first intercourse that symptoms began, mos	47.7	30.7	0.11
Mean Number of Sexual Partners	2.79	2.46	0.36
Recent Pregnancy	8 (10.1%)	4 (4.7%)	0.18
Recent Gynecological Operation	3 (3.8%)	4 (4.7%)	0.79
Atopy	46 (58.2%)	36 (41.8%)	0.06
Prior Skin prick test (SPT)	24 (30.4%)	24 (27.9%)	0.73
Reports dog sensitization	9 (11.4%)	2 (2.3%)	0.02
Food Allergy	30 (38%)	22 (25.9%)	0.10
Drug Allergy	35 (44.3%)	26 (31%)	0.08
Chronic Candidiasis	34 (43%)	35 (41.2%)	0.81
Time after intercourse that reactions occur, min	94.1	188.3	0.41
Time Reactions Last, min	2947.2	2106.5	0.28

Sublet W, Bernstein JA. Allergy Asthma Proc 2011;32:467-71.





Sublet W, Bernstein JA. Characterization of patients with suspected seminal plasma hypersensitivity. Allergy Asthma Proc 2011 Nov-Dec;32(6):467-71.

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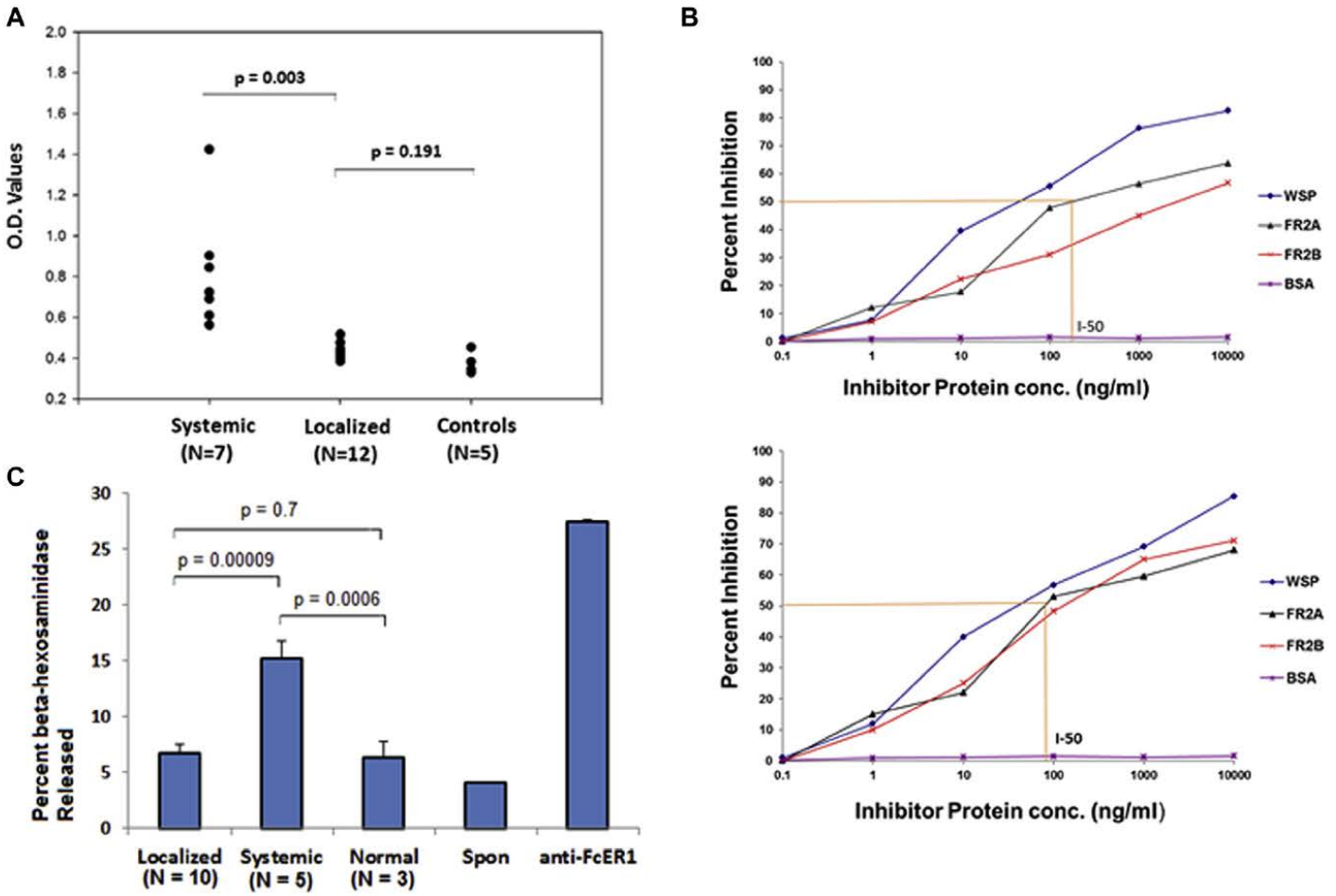
Specific IgE, ELISA inhibition and Beta-hexosaminidase Assessment of Systemic And Localized SPH



Ghosh D, Bernstein JA. JACI 2014; 134:969-972.

TABLE I. Clinical, immunologic, and therapeutic characteristics of women with systemic and localized SPH

Characteristic	Systemic SPH	Localized SPH
Symptoms	Urticaria, chest tightness, wheezing, diarrhea, dizziness, rarely vascular collapse*	Vaginal pain, burning, swelling; ± localized pruritus
Symptoms with use of a condom	No	No
Skin prick testing result to WSP	Positive	Negative†
Specific IgE to SPPs	Positive	Equivocal to negative
Basophil histamine release	Positive	Negative
T_H2 -> T_H1 shift after desensitization	Yes	No
Therapeutic response after desensitization	Yes	Yes, but response is sometimes incomplete
Able to conceive	Yes	Yes

*May also experience localized symptoms.
†Intracutaneous testing using WSP is not recommended because of irritant-induced responses.

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Ghosh D, Bernstein JA. JACI 2014; 134:969-972.

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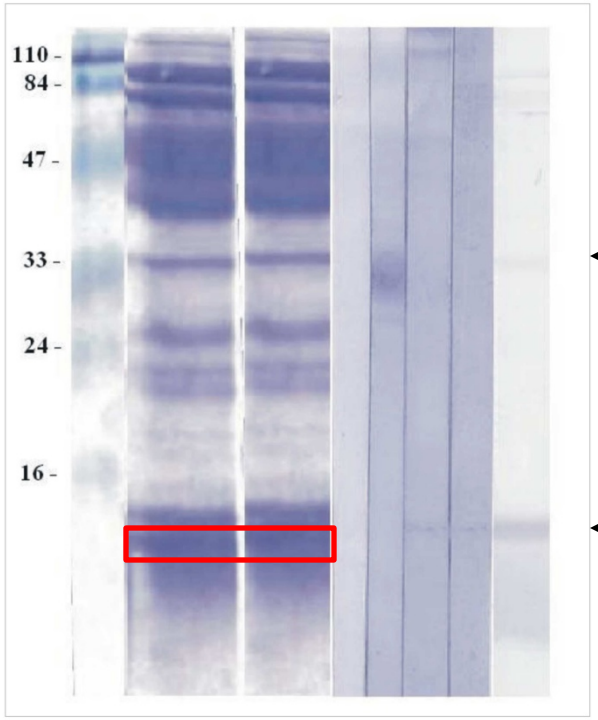
PSA is a relevant seminal plasma allergen in patients with SPH



M: Position of markers
S1 and S2: SDS-PAGE of whole seminal plasma (WSP) from two donors
C-Specific IgE Immunoblot using serum from normal donor
Columns1 through 4: Specific IgE Immunoblots using sera from four HSP patients

The 32 kD band has been identified as PSA immunoblotting using an anti-PSA Mab.
The 10 kD band may be a fragment of PSA

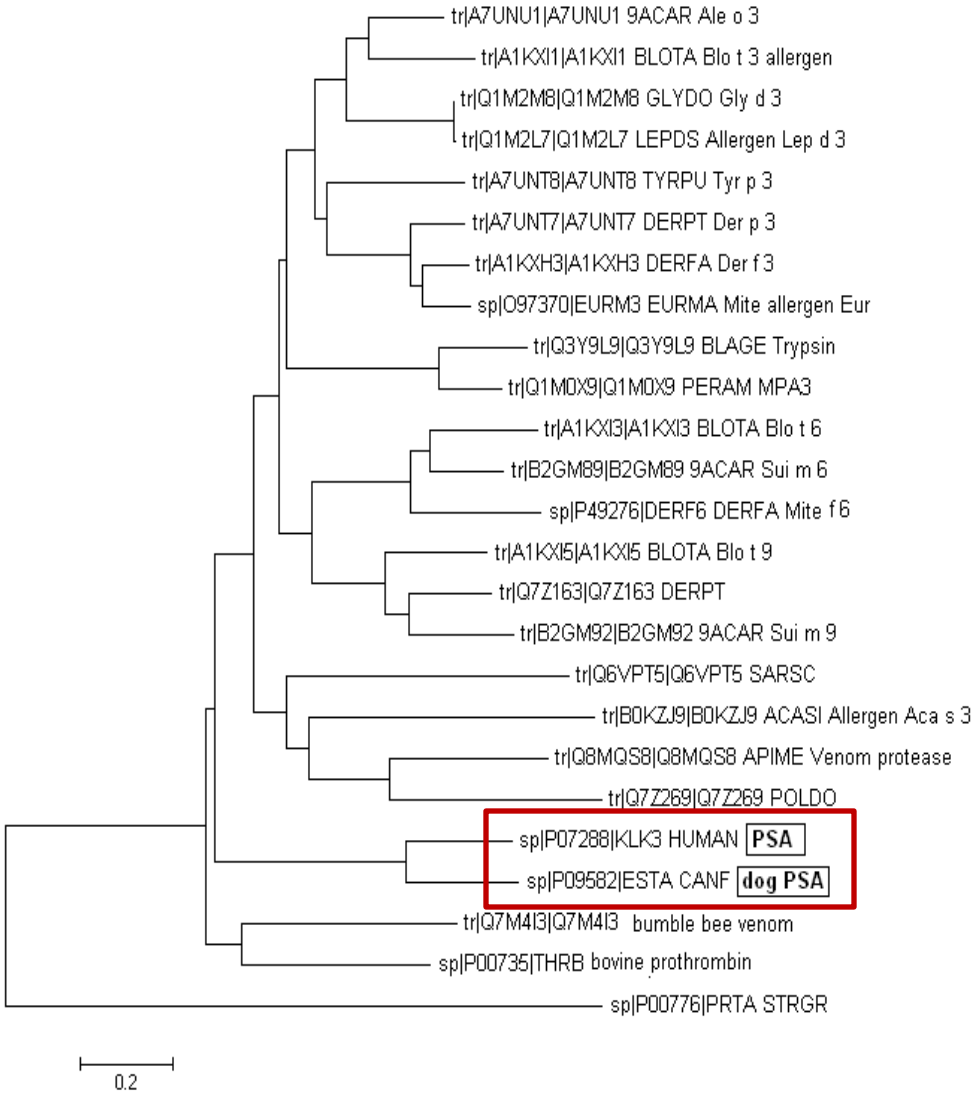
Patient sera show different binding patterns; Columns 2, 3 and 4 recognize the 10kD band while 1 and 4 recognize the 32kD band.

Cross Reactivity With Other Common Allergens May Explain Symptoms After First Time Intercourse

- 30-40% of women report symptoms after first exposure to seminal fluid
  - suggests the existence of a cross-reactive pre-sensitizing allergen
- Basagana et.al. reported cross reactivity among dog dander proteins and PSA.
- ? Similar response as pollen food allergy syndrome

Bernstein JA, et.al. Ann Allergy Asthma Immunol 1997; 78:54-8.
Basagana M, et.al. JACI 2008; 121:233-9.

Dendrogram showing evolutionary relationship between all the known serine protease allergens



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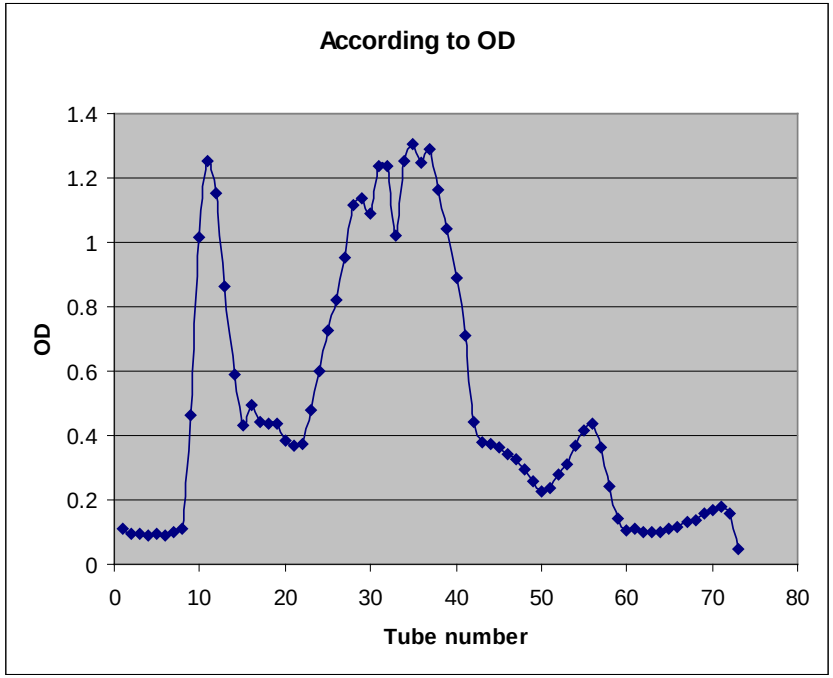
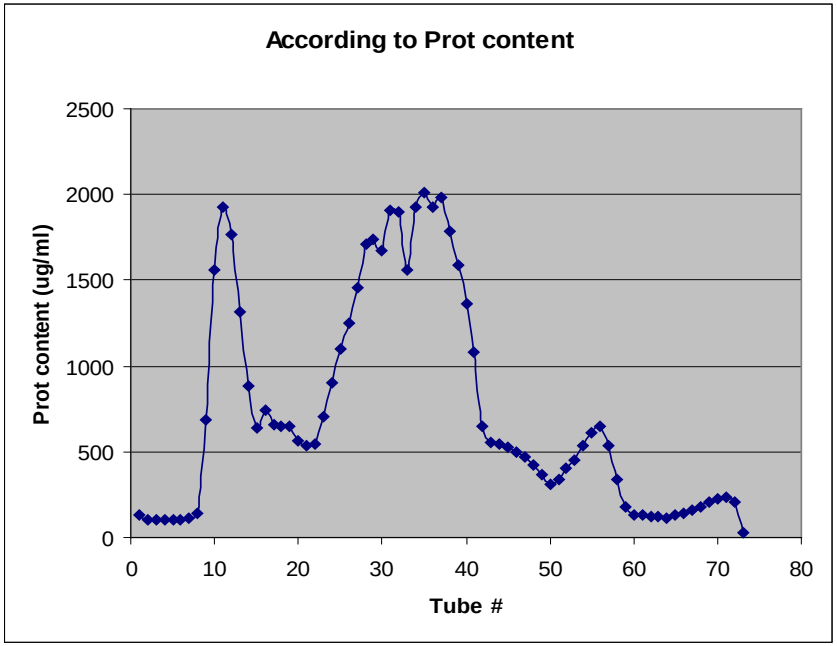
Treatment

- Avoidance
- Antihistamine (H1 and H2), LTMA, NSAIDS – often ineffective
- Graded intravaginal challenge using whole seminal plasma
  - First line treatment and usually effective
  - Less time consuming, less expensive and easier to administer
- Subcutaneous desensitization using relevant SPPs
  - Effective for both systemic and localized SPH

Bernstein JA, et.al. Obste Gynecol 1993; 82:667,
Bernstein IL, et.al. Contrib Gynecol Obste 1985; 14:151.

FPLC Fractionation of Whole Seminal Fluid





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Flow Cytometric Analysis of CD4+ T cells Pre- and Post-SPP Desensitization in Women with Systemic and Localized SPP

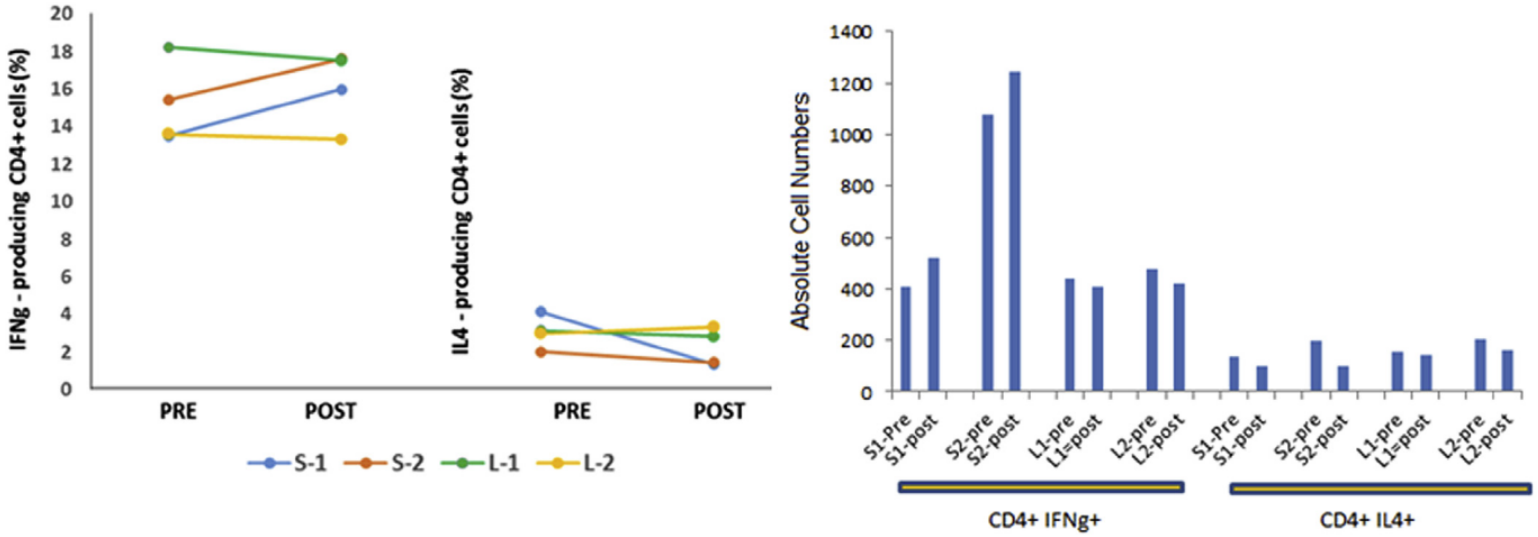

FIG E1. Flow cytometric analysis of $CD4^+$ T-cell population before and 18 hours after SPP desensitization of women with systemic (S1 and S2; n = 2) and localized (L1 and L2; n = 2) SPH. IFN-γ–producing $CD4^+$ cells were expressed as percentage of $CD4^+$ cells (left panel). Absolute numbers of cells is also illustrated (right panel). A modest increase in IFN-γ–producing $CD4^+$ cells and a modest decrease in IL-4–producing $CD4^+$ cells were found for the systemic, but not localized, reactors.

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Ghosh D, Bernstein JA. JACI 2014; 134:969-972.

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Seminal Plasma Hypersensitivity and Fertility

- Women with localized and systemic SPH are able to conceive
  - Intrauterine insemination using washed spermatozoa to remove sensitizing proteins
  - In vitro fertilization
  - Natural intercourse
    - post-desensitization to relevant seminal plasma proteins

Resnick DJ, Hatzis DC, Kanganis P, Liccardi FL, Lee-Wong M, Bernstein JA.
Am J Reprod Immuno 2004 Jul;52(1):42-4.
Tan J, Bernstein JA. Letters / Ann Allergy Asthma Immunol 111 (2013) 138e148.

Burning Semen Syndrome

- Gulf War veterans returning from the first Gulf War conflict (1990-1991) began reporting burning after ejaculation
- In some cases this caused localized vaginal burning and pain for their female sexual partner
- We were funded by the DOD to investigate this problem
  - Distributed questionnaire surveys to 188 GW veterans with suspected BSS
  - 7% had preexisting symptoms
  - <50% of their sexual partners had resolution of symptoms after use of a condom excluding SPH
- Dividing questionnaire respondents into “healthy” and “unhealthy” groups based on the absence or presence of multiple physical symptoms revealed a significant correlation between the “unhealthy” group and PTSD

Bernstein JA, et.al. Obstet Gynecol 2003; 101:93-102.

Burning Semen Syndrome

- Five couples in the “healthy” group met the criteria for SPH and were treated with SPP desensitization
  - Three couples had complete resolution of symptoms
  - One couple had partial resolution
  - One couple without response

Bernstein JA, et.al. Obstet Gynecol 2003; 101:93-102.

Burning Semen Syndrome

- BSS evaluation was hindered by
  - Poor case definition of the underlying problem
  - Multiple concomitant somatic and psychological symptoms hindering a focused evaluation
  - Logistical difficulties in evaluating geographically dispersed individuals throughout the study
- Possible variant of localized SPH?

Bernstein JA, et.al. Obstet Gynecol 2003; 101:93-102.

Proposed Mechanisms For Systemic and Localized SPH

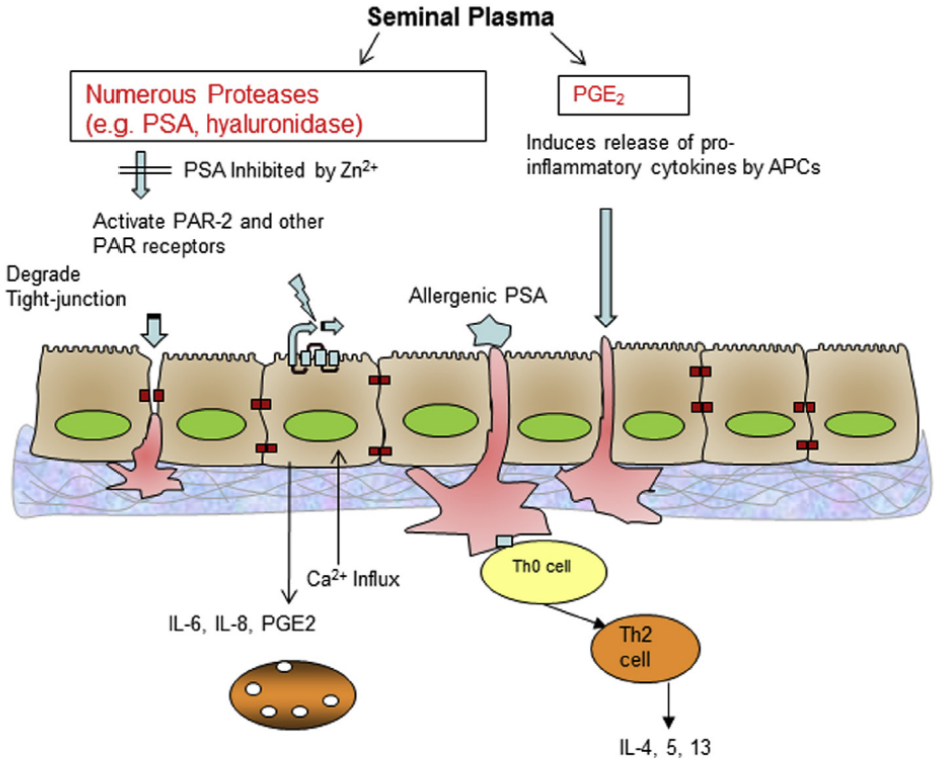

FIG E2. Postulated mechanisms for localized SPH: Although women with systemic SPH sensitized to PSA can induce a specific serum IgE response through the classical T_H2 pathway, women with localized SPH may exhibit symptoms as a result of seminal plasma proteases causing degradation of mucosal tight junctions, leading to the activation of PAR-2 receptors on epithelial cells that results in the release of proinflammatory cytokines and localized inflammation. Seminal plasma also contains high levels of prostaglandin E2 (PGE_2), which can activate antigen-presenting cells (APCs) lining the inner face of the vaginal epithelium, leading to the release of proinflammatory cytokines, causing localized mucosal inflammation.

Ghosh D, Bernstein JA. JACI 2014; 134:969-972.

Case Study 2

- 28 year old female presents with recurrent vulvovaginal yeast infections confirmed by culture
- Responsive to topical and systemic anti-fungal agents but the infections reoccur
- Very debilitating causing significant interpersonal strain on her current relationship
- Past medical history unremarkable for diabetes, use of OCP or hormones in general as a birth control and no use of antibiotics
- Symptoms persist regardless of using a condom donned before intercourse
- Specific IgE and SPT to *Candida albicans* were positive

Diagnosis: Chronic Vulvovaginal Candida Hypersensitivity

Candida Vaginal Infections

- 75% of females experience at least one yeast infection
- Recurrent infections more common in women with diabetes, on oral contraceptives or taking antibiotics
  - Most women have no recognizable risk factors
- Pathogenesis is unclear
  - Abnormal macrophage responses to *Candida albicans* resulting in increased PGE2 which inhibits lymphocyte responses to *Candida*
  - Anti-*C. Albicans* IgE antibodies and PGE2 are increased in vaginal fluid of women with recurrent vaginal candidiasis
  - Vaginal hypersensitivity to *Candida albicans* may be caused by increased levels of PGE2 which can suppress localized vaginal cell-mediated immune responses resulting in yeast colonization and recurring infections

Bernstein JA. Immunologic Disorders of the Female and Male Reproductive Tracts. Ann Allergy Asthma Immunol 108 (2012) 390–395.

Vulvovaginal Candida Hypersensitivity

- Recurrent vaginal candida infections
  - Culture proven
  - No identifiable cause
  - Not responsive to topical or systemic antifungal therapy
  - Positive sIgE antibody to *Candida albicans*
- Rigg et.al. treated 18 women with recurrent vaginal candidiasis with subcutaneous immunotherapy to *C. albicans*
  - 79% experienced a decrease in the mean # of vaginitis episodes after one year of treatment (17.2±2 to 4.3±1.8; p<.0004)
- Other case reports/case series have confirmed these observations
- No double blind placebo controlled study

Bernstein JA. Immunologic Disorders of the Female and Male Reproductive Tracts. Ann Allergy Asthma Immunol 108 (2012) 390–395.

Chronic vulvovaginal *Candida* hypersensitivity: An underrecognized and undertreated disorder by allergists

Table 1. Clinical characteristics of women with recurrent vulvovaginal *Candida* hypersensitivity treated with *Candida* immunotherapy

Age	Race	OCP	DM	Worse With Abx	Skin Test	Atopy	LPR	Total IgE (IU/mL)	Specific IgE (IU/mL)	Culture (+) for *Candida*
40	C	N	N	N	ID	Y	+	ND	ND	+
15	C	Y	N	Y	ID	N	+	<18	<18 IU/mL	+
62	C	N	N	N	ID	N	+	ND	ND	+
26	C	N	N	Y	ID	Y	+	ND	ND	+
34	C	N	N	Y	ID	N	+	ND	<18 IU/mL	+
29	C	N	N	Y	ID	Y	+	64	ND	+
48	C	N	N	Y	ID	N	+	55	<18 IU/mL	+
41	C	N	N	Y	PST	N	+	47	ND	+
30	C	N	N	Y	ID	N	+	ND	ND	+
40	C	N	N	Y	ID	N	+	ND	ND	+
64	C	N	N	N	ID	N	+	ND	ND	+
40	C	N	N	N	ID	N	+	28	ND	+

OCP = oral contraceptive (none of the postmenopausal women were using hormone replacement therapy); DM = diabetes mellitus; ID = intradermal; PST = prick skin test; LPR = late phase response; ND = not done; Abx = antibiotics.

Table 2. Clinical endpoints of women with recurrent vaginal candidiasis treated with *Candida* immunotherapy

Maximum Immunotherapy Concentration	Months on Immunotherapy	Total Symptom Scores Pre→Post Immunotherapy
1:1000	66‡*	9→3
1:1000	33‡*	9→0
1:1000	30‡*	9→0
1:1000	86	9→3
1:1000	16*†	9→3
1:500	12*†	9→3
1:5000	21*†	9→3
1:10,000	2‡	9→9
1:1000	17	9→3
1:1000	9	9→3
1:50,000	39	9→0
1:1000	91	9→0

** Denotes patient currently still on immunotherapy.*
† Denotes patient lost to follow-up.
‡ Denotes patient cessation due to reaction.

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Bernstein JA, Seidu L. Allergy Rhinol 2015; 6:e44 –e49.

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Case Study 3

- 35 year old healthy male presents with a constellation of symptoms including low grade temperatures, generalized fatigue, malaise and severe memory and concentration difficulties occurring immediately after ejaculation which lasts for 5-7 days
- Onset of symptoms one year prior
- Past medical history unremarkable - No history of allergies or asthma
- Sexual partner without symptoms
- Treatment with NSAIDs and antihistamines OTC unremarkable

Postorgasmic Illness Syndrome

- In 2002 men began reporting severe fatigue, low grade fevers, upper respiratory symptoms , concentration difficulties, irritability, and flu like symptoms after ejaculation
- Criteria for diagnosis based on demographic characterization of 45 men with POIS are:
  - A flulike state, extreme fatigue or exhaustion, muscle weakness, mood disturbances/irritability, memory/concentration difficulties, incoherent speech, nasal congestion, rhinorrhea and ocular itching
  - Immediate or slightly delayed onset of symptoms after ejaculation
  - Occurrence in more than 90% of ejaculation events
  - Duration for 2-7 days
  - Spontaneous resolution
- Pathogenesis and treatment unknown
  - niacin helpful in some
  - 2 case reports of males being desensitized to own semen

Waldinger MD, et.al. J Sex Med 2011; 8:1164-1176.

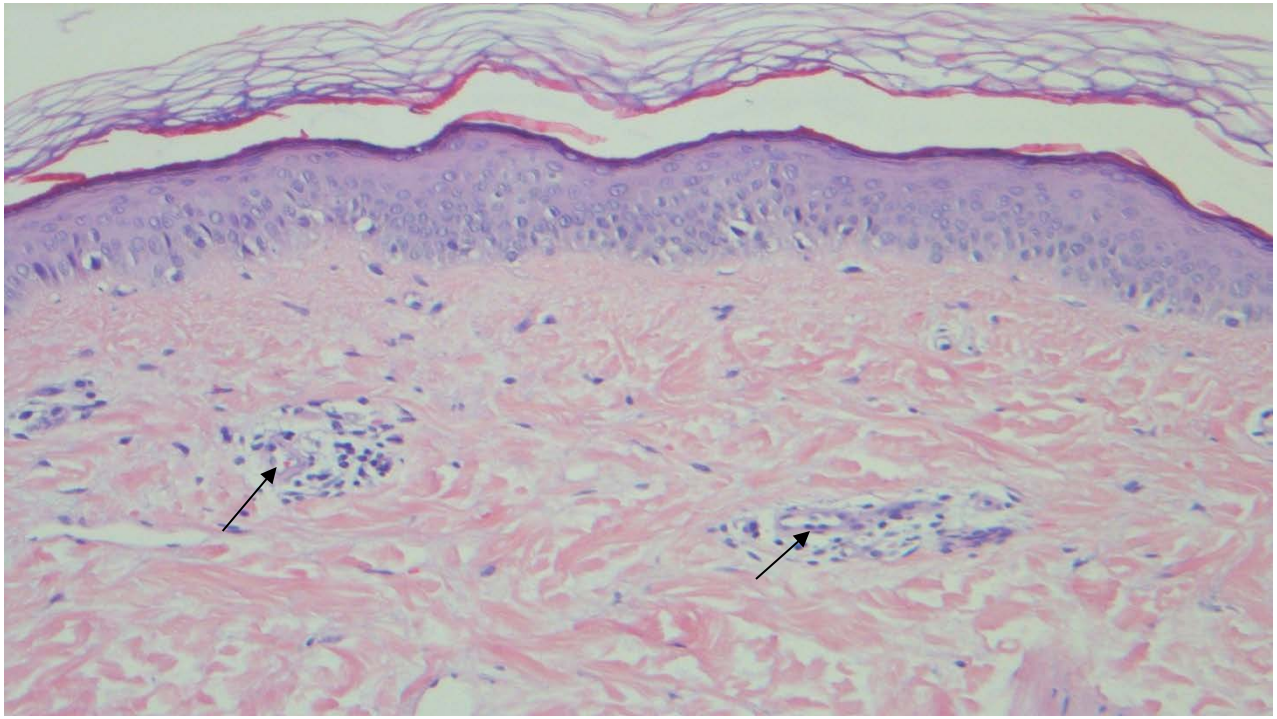
Case Study #3

APD Presenting As Cyclic Urticaria/Angioedema, Dermatitis and Anaphylaxis

- 26 year old female with 6 month history of oligomenorrhea and polycystic ovary disease presents with facial angioedema, bronchospasm and hypotension within 2 days of starting Ortho-Novum 777 (norethindrone + ethinyl estradiol) prescribed to prevent the recurrence of rupturing cysts
  - The OCP was discontinued for 1 week and restarted 2 weeks later resulting in a similar reaction
  - Three subsequent reactions over a 2 month period each with increasing intensity and duration
- History revealed the occurrence of premenstrual urticaria with angioedema
- Skin prick testing to progesterone, 5β- pregnanediol, estradiol, norethindrone and ortho-novum-777 were negative
- Leukocyte histamine release demonstrated positive response to 5β- pregnanediol which decreased four months after discontinuing OCP
- Condition completely resolved after several years of treatment with naferelin

Bernstein IL, et.al. J Women's Health 2011; 20:643-644.

Histopathology



*Note perivascular accumulation of lymphocytes in the dermis (black arrows). This finding is nonspecific but is consistent with either a drug reaction or APD.

Bernstein IL, et.al. J Women's Health 2011; 20:643-644.

Presentations of Autoimmune Progesterone Dermatitis

Anaphylactoid reactions
- Premenstrual
- Catamenial

Dermatologic/mucosal reactions
- Stomatitis
- Eczema
- Erythema multiforme
- Stephens-Johnson syndrome
- Fixed drug eruptions
- Folliculitis
- Vesiculobullous reactions
- Urticaria
- Urticaria and angioedema

*More than one of these presentations can occur together

Snyder JL, Krishnaswamy G. Ann Allergy Asthma Immunol 2003;90:469-77.
Bernstein IL, et.al. J Women's Health 2011; 20:643-648.

Catamenial Anaphylaxis

- Varies from APD by timing of symptoms
  - Begins at the start of the menstrual flow
  - Continues throughout the menstrual flow
  - Symptoms stop when menstrual flow stops
- Endometrial derived mediators such as $PGF_2\alpha$ may leak into the systemic circulation causing these reactions
  - Indomethacin has helped in some cases
- Skin testing and intramuscular hormone challenge tests are usually negative
- Symptoms resolve with BSO

Snyder JL, Krishnaswamy G. Ann Allergy Asthma Immunol 2003;90:469-77.

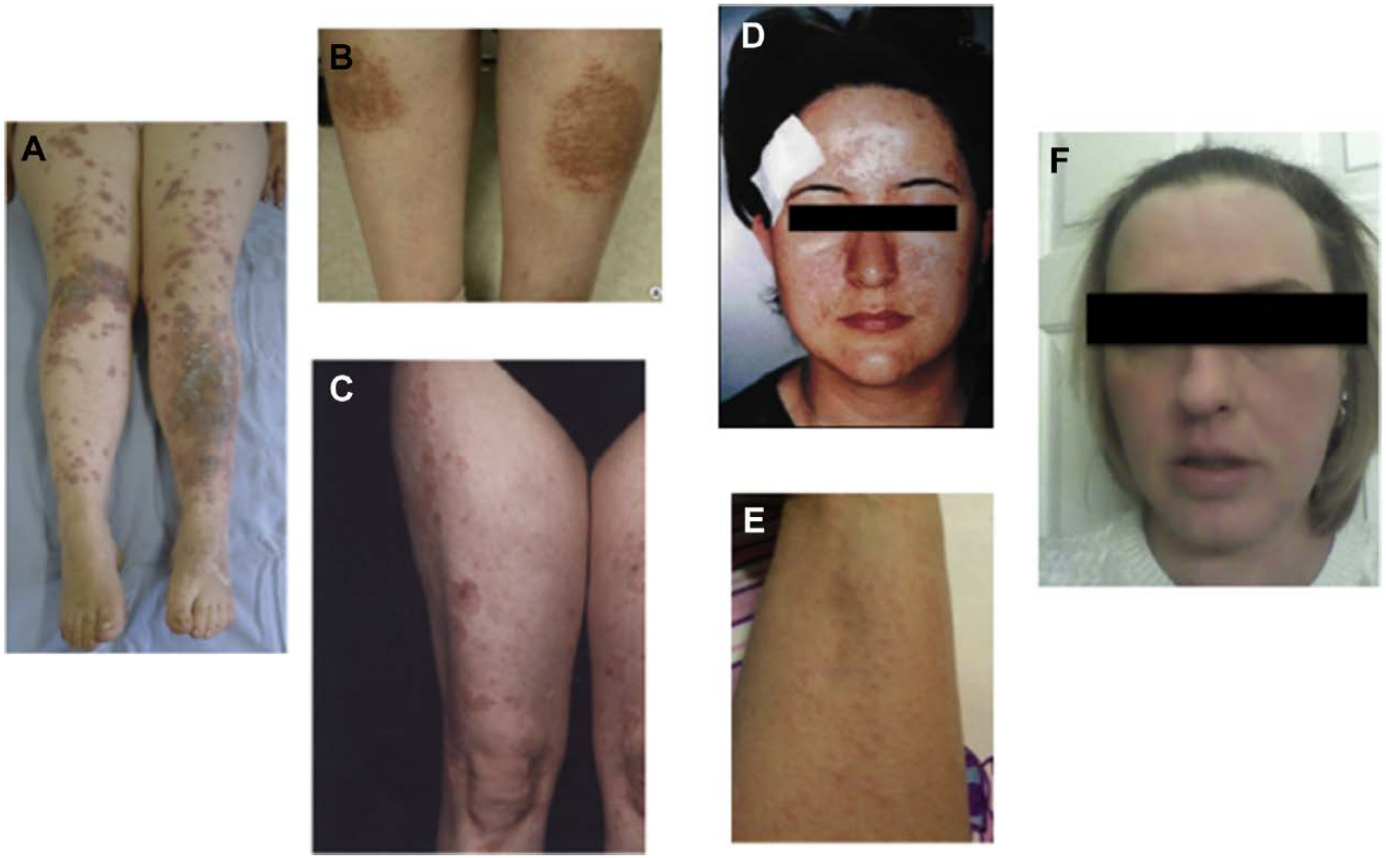


FIGURE 2. The polymorphic cutaneous manifestations of progestogen hypersensitivity. **A**, Pustules and plaques; **B**, nummular eczematous dermatitis; **C**, annular targetoid plaques; **D**, maculopapular rash; **E**, eczematous dermatitis; and **F**, angioedema/urticaria.

Diagnosis of APD

- History
  - Cyclic skin lesions related to the menstrual cycle
  - Onset usually in adult life after menarche, but can occur or worsen during pregnancy
  - Symptoms start 3-10 days before premenstrual flow and cease 1-2 days into the menses
  - Skin manifestations without or with systemic manifestations
- Physical exam
  - Presentation of skin rashes in different morphological forms
- In vivo or in vitro testing:
  - A positive progesterone skin test?
  - A positive oral/intramuscular challenge to progesterone?
  - Demonstration of a circulating antibody to progesterone?
  - Basophil degranulation tests?

Diagnostic Testing

- ELISA
  - Optimization of these assays require that a conjugated preparation of progesterone rather than a progesterone hapten alone be used
- Skin testing using aqueous preparations of progesterone preferred
  - Progesterone in oil can cause an irritant response
  - Positive skin tests typically occur within 30 minutes consistent with an early phase response (Type I immune response)
  - Delayed reactions with erythema and induration peak at 24 and 48 hours consistent with late phase response (Type IV immune response)
  - Many case reports using progesterone skin testing to diagnose APD have used high progesterone concentrations and were performed without appropriate solvent controls or did not establish sub-irritant levels in normal controls

Conclusions: Skin testing and Immunoassays are not standardized and therefore not reliable as predictors for progesterone induced hypersensitivity

Herzberg AJ, et.al. J Am Acad Dermatol 1995; 32: 335-8.

Specific IgE to Progesterone Assay

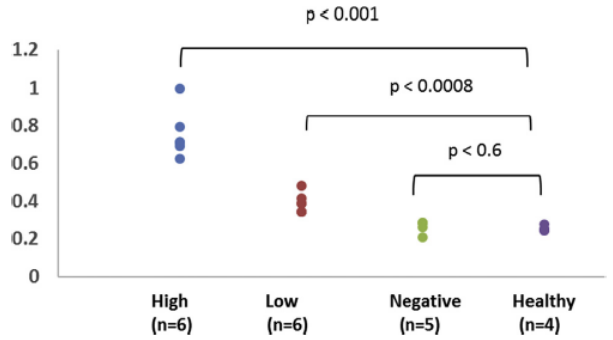


Figure 2. Single-batch progesterone-specific IgE ELISA optical density (OD) results using sera from patients with suspected PH in Table 1 demonstrating distribution of high, low, and negative cut points for the assay. (High positive = OD > 2 × OD cutoff; low positive = >1 × OD + 3 SD to <2 × OD + 3 SD; negative = ≤1 × OD + 3 SD). Four serum samples collected from healthy nonatopic subjects were used as negative controls. ELISA, enzyme-linked immunosorbent assay; OD, optical density; PH, progesterone hypersensitivity.

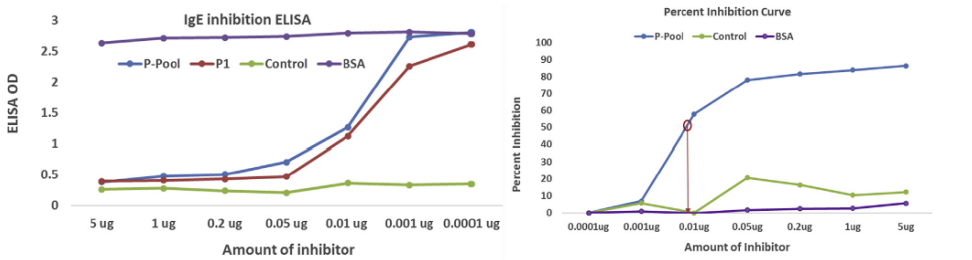


Figure 3. ELISA inhibition using serum samples from high positive PH patients and healthy nonatopic controls. (A) Left panel: Progesterone-BSA conjugate was added to either a pooled serum sample of high positive progesterone–sensitized patients (n = 5; P = Pool, blue line) or to an individual high positive patient serum sample (P1; red line) vs an individual negative control serum (Control; green line). Dose-dependent inhibition of IgE reactivity was observed for patients' sera (pooled and individual), but not for negative control serum or unconjugated BSA (BSA; pink line). (B) Right panel: Plot shows the calculated percent inhibition for the pooled sera, indicating dose-dependent inhibition of IgE binding by progesterone-BSA (P = pool, blue line; approximately 10 ng progesterone-BSA was enough for 50% inhibition, red arrow), whereas nonatopic control sera supplemented with progesterone-BSA (Control; green line) or pooled PH sera supplemented with unconjugated BSA (BSA; purple line) does not show significant inhibition. BSA, bovine serum albumin; ELISA, enzyme-linked immunosorbent assay; PH, progesterone hypersensitivity.

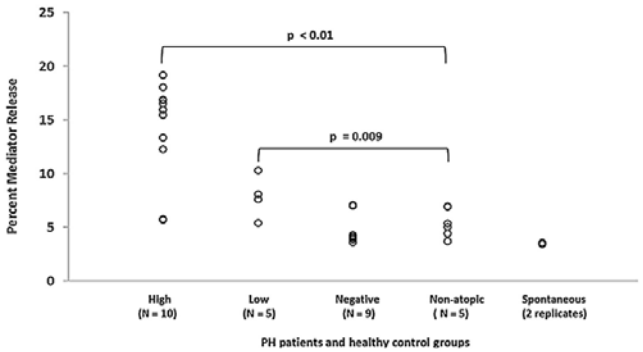


Figure 4. Results of a beta-hexosaminidase mediator release assays using patient sera with suspected PH previously found to be high positive, low positive, and negative for progesterone sIgE by direct ELISA. Spontaneous release is defined as mediator release without progesterone-BSA exposure. Two ELISA-high sera failed to induce significant mediator release. ELISA-high and ELISA-low groups induced significantly higher mediator release compared with the nonatopic control group. BSA, bovine serum albumin; ELISA, enzyme-linked immunosorbent assay; PH, progesterone hypersensitivity.

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Ghosh D, Bernstein JA. Development of a progesterone-specific IgE assay for diagnosing patients with suspected progestogen hypersensitivity. Ann Allergy Asthma Immunol. 2019 Jun;122(6):616-622.

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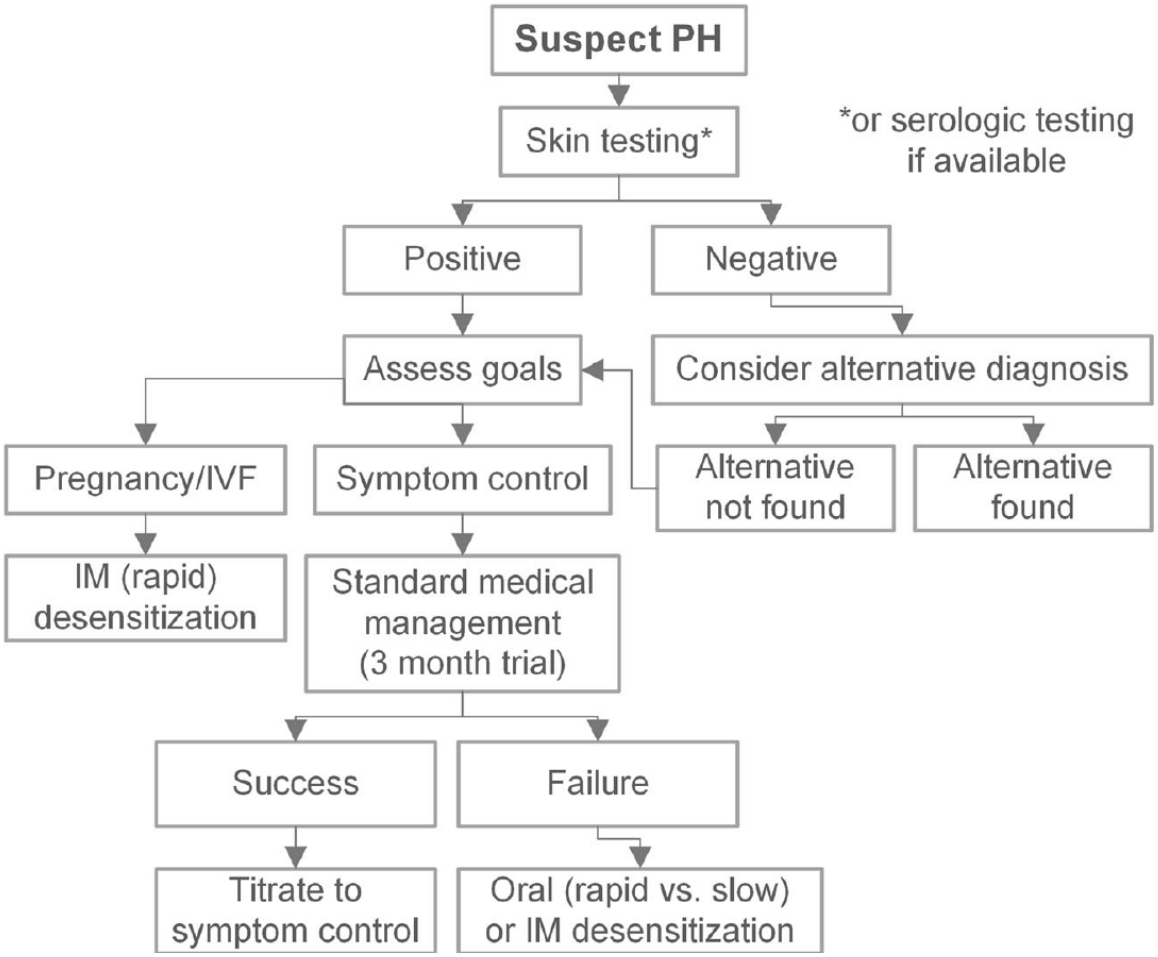

department of Internal Medicine

Buchheit K, Bernstein JA. JACI: In Practice 2017; 5: 566-574.

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Treatment Options For APD

TABLE III. Treatment options in progestogen hypersensitivity

Treatment category	Drug class	Potential problems
Symptomatic relief	Oral antihistamines	Incomplete efficacy
	Topical glucocorticoids	Incomplete efficacy
	Systemic glucocorticoids	Incomplete efficacy, long-term side effects
Ovulation suppression	Combined oral contraceptive pills	Possible hypersensitivity reaction to low-dose progesterone
	GnRH agonists (ie, leuprolide)	Estrogen withdrawal symptoms
	Selective estrogen-receptor modulators (ie, tamoxifen)	Estrogen withdrawal symptoms
	17-α-Alkylated steroids (ie, stanozolol, danazol)	Hirsutism, mood changes, LFT abnormalities
	Oophorectomy	Premature menopause, permanent loss of fertility
Desensitization	Rapid desensitization to oral, IM, or intravaginal progestogens	Resource intensive, risk of hypersensitivity reactions during desensitization
	Slow desensitization to oral progestins	Risk of hypersensitivity reactions during desensitization

GnRH, Gonadotropin-releasing hormone; *IM*, intramuscular; *LFT*, liver function test.

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Desensitization Protocols

Table 1 Oral and intramuscular progestin desensitization protocols. A Oral protocol. B Two-day oral protocol. C Rapid IM protocol. *IM* intramuscular, *IVF* in vitro fertilization. Reproduced with permission from Buchheit [25••] which is originally from Foer et al. [23] and Prieto-Garcia et al. [6••]

A

Day	Dose (based on progestion component)	Number of capsules × capsule dose per day	Total daily dose
Day 1	1.25 μg in AM, 2.5 μg in PM	1 × 1.25 μg; 2 × 1.25 μg	3.75 μg
Day 2	2.5 μg in AM, 12.5 μg in PM	2 × 1.25 μg; 1 × 12.5 μg	15 μg
Day 3	12.5 μg in AM, 25 μg in PM	1 × 12.5 μg; 2 × 12.5 μg	37.5 μg
Day 4	37.5 μg in AM, 37.5 μg in PM	3 × 12.5 μg; 3 × 12.5 μg	75 μg
Day 5	50 μg in AM, 37.5 μg in PM	1 × 50 μg; 1 × 50 μg; 2 × 12.5 μg	125 μg
Day 6	250 μg	2 × 125 μg	250 μg
Day 7	500 μg	4 × 125 μg	500 μg
Day 8	500 μg	4 × 125 μg	500 μg
Day 9	1 mg	1 × 1 mg	1 mg

Target dose for this period. Norethindrone 1 mg/ ethinyl estradiol 0.02 mg

B

Time (h)	Dose
00:00 (first day)	0.1mg
00:45	1 mg
01:30	5 mg
02:15	10 mg
03:00	25 mg
00:00 (next day)	50 mg
00:45	100 mg
01:30	100 mg

C

Time	Dose IM progesterone 50 mg/mL
0 min	1 mg
30 min	2 mg
60 min	4 mg
90 min	8 mg
120 min	16 mg
150 min	18.5 mg
Total dose	50 mg
Target daily dose	Intravaginal Progesterone 90-180 mg (i.e., 8% gel once or twice daily) or IM progesterone 50-75 mg daily, depending on IVF protocol

*case reports, case series using omalizumab alone to treat or adjunctively with desensitization

Conclusions

- Allergists should be familiar with allergic disorders involving the reproductive systems in women and men
- Clinical presentations can be quite variable
- Diagnostic testing has limitations for some conditions (i.e., PH, POIS) – unmet need
- Pathomechanisms for localized SPH and POIS require further evaluation
- Treatment for most conditions except POIS is usually successful

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???Questions???