



CME Review

Cyclical hypersensitivity, anaphylaxis, and related hormonal reaction



William J. Lavery, MD, PhD; Jonathan A. Bernstein, MD

Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, Cincinnati, Ohio

ARTICLE INFO

Article history:

Received for publication October 4, 2018.

Received in revised form November 14, 2018.

Accepted for publication November 14, 2018.

Key Messages

- Although endogenous or exogenous exposure to progesterone or estrogen that induce a spectrum of hypersensitivity reactions and/or other skin eruptions are believed to be uncommon, their prevalence is currently unknown.
- Clinical manifestations are heterogeneous but typically involve cyclical manifestation of a spectrum of dermatitis conditions and/or systemic symptoms.
- Diagnosis is made primarily by history in conjunction with in vitro assays to measure specific IgE and provocation challenge testing when appropriate; judicious use of skin testing is recommended because of their irritant-causing effects.
- Pathomechanisms are incompletely understood but likely involve IgE-mediated immediate-type hypersensitivity.
- Treatment is aimed at symptomatic control with nonsedating histamine₁ antihistamines, short-term use of systemic glucocorticoids, progesterone desensitization, and/or suppression of ovulation by a pharmacologic or, as a last resort, surgical approach.

Instructions

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
- Read the article and reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned. At this time, physicians will have earned up to 1.0 AMA PRA Category 1 CreditTM. Minimum passing score on the post-test is 70%.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Reprints: Jonathan A. Bernstein, MD, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML 563, Cincinnati, OH 45267-0563; E-mail: jonathan.bernstein@uc.edu.

Disclosures: The authors report no conflicts of interest.

Funding Sources: None.

<https://doi.org/10.1016/j.anai.2018.11.016>

1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Define the 3 main identified types of cyclical hypersensitivity and appreciate their clinical presentations.
- Describe the proposed etiology and pathomechanisms of cyclical hypersensitivities.
- Discuss how to diagnose and treat cyclical hypersensitivity disorders.

Release Date: February 1, 2019

Expiration Date: January 31, 2021

Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

Accreditation

The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation

The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Policy

As required by the Accreditation Council for Continuing Medical Education (ACCME) and in accordance with the American College of Allergy, Asthma and Immunology (ACAAI) policy, all CME planners, presenters, moderators, authors, reviewers, and other individuals in a position to control and/or influence the content of an activity must disclose all relevant financial relationships with any commercial interest that have occurred within the past 12 months. All identified conflicts of interest must be resolved and the educational content thoroughly vetted for fair balance, scientific objectivity, and appropriateness of patient care recommendations. It is required that disclosure be provided to the learners prior to the start of the activity. Individuals with no relevant financial relationships must also inform the learners that no relevant financial relationships exist. Learners must also be informed when off-label, experimental/investigational uses of drugs or devices are discussed in an educational activity or included in related materials. Disclosure in no way implies that the information presented is biased or of lesser quality. It is incumbent upon course participants to be aware of these factors in interpreting the program contents and evaluating recommendations. Moreover, expressed views do not necessarily reflect the opinions of ACAAI.

Disclosure of Relevant Financial Relationships

All identified conflicts of interest have been resolved. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted.

Planning Committee

- Jonathan A. Bernstein, MD (Annals CME Subcommittee): Consultant, Fees: Imedics; Consultant/Principal Investigator, Grants/Fees: Boehringer Ingelheim, GlaxoSmithKline; Consultant/Principal Investigator/Speaker, Grants/Fees: AstraZeneca, CSL Behring, Novartis/Genentech, Shire; Speaker, Fees: Baxalta
- Guha Krishnaswamy, MD (Annals CME Subcommittee): Clinical Research, Grant: CSL Behring
- Gailen D. Marshall, Jr, MD, PhD (Editor-in-Chief): Clinical Research, Grants: Sanofi, Stallergenes
- Anna Nowak-Wegryzyn, MD (CME Series Editor, Deputy Editor): Clinical Research, Grant: Nutricia, Nestle, ITN NIH, DBV, Astellas; Speaker, Fees: Nutricia, Nestle, Thermofisher; Contributor, Royalties: UpToDate; Clinical Trial DMC Member: Merck; Board Member: Gerber, IFPIES
- John J. Oppenheimer, MD (Annals CME Subcommittee, Associate Editor): Consultant, Other financial gains: DBV Technologies, GlaxoSmithKline, Kaleo; Clinical Research, Grants: AstraZeneca, Boehringer Ingelheim, Novartis

Authors

- Jonathan A. Bernstein, MD; Consultant/Private Investigator, Grants/Fees: Allakos; Private Investigator/Speaker/Consultant, Grants/Fees: AstraZeneca; Private Investigator, Grants/Fees: Genentech/Novartis
- William J. Lavery, MD, PhD has no relevant financial relationships to disclose.

Recognition of Commercial Support: This activity has not received external commercial support.

Copyright Statement: ©2015–2019 ACAAI. All rights reserved.

CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

Introduction

A 16-year-old girl presented with recurring cyclical erythematous pruritic persistent rash that had vesicles at times, lip swelling, dizziness, tingling and burning on face and lips, hands tingling, and chest tightness for the past 2 years. The symptoms typically began 2 to 3 days before the onset of her menstrual cycle and continue into the cycle for 3 to 4 days before dissipating. However, because of the irregular nature of her cycles, which were treated with an oral estrogen-progestogen contraceptive pill, she sometimes noticed the onset of symptoms 1 or 2 days after the onset of her flow. Her symptoms were not alleviated with standard combination therapy, including maximum doses of histamine₁ (H1) antihistamines, an H₂-antihistamine, and a leukotriene receptor antagonist. Because of the cyclical nature of her symptoms, a serum specific IgE assay to progesterone was performed, which revealed elevated levels. A trial

of leuprolide resolved her symptoms, confirming the diagnosis of progesterone hypersensitivity (PH). Progesterone desensitization was attempted but was not tolerated because of the above recurring symptoms despite a gradual, slow up-dosing schedule during a 6-month period. Subsequently, subcutaneous injections of 300 mg of omalizumab were started every 4 weeks, which allowed her to tolerate progesterone desensitization. Currently, she remains symptom free on standard combined oral contraceptive pills.

Background

Most cases of hypersensitivity or anaphylaxis are the direct result of isolated, exogenous exposure to a culprit allergen. In some circumstances, endogenous or exogenous exposure to allergen can present as cyclical organ-specific hypersensitivity or as systemic anaphylaxis. Examples include progestogen hypersensitivity,

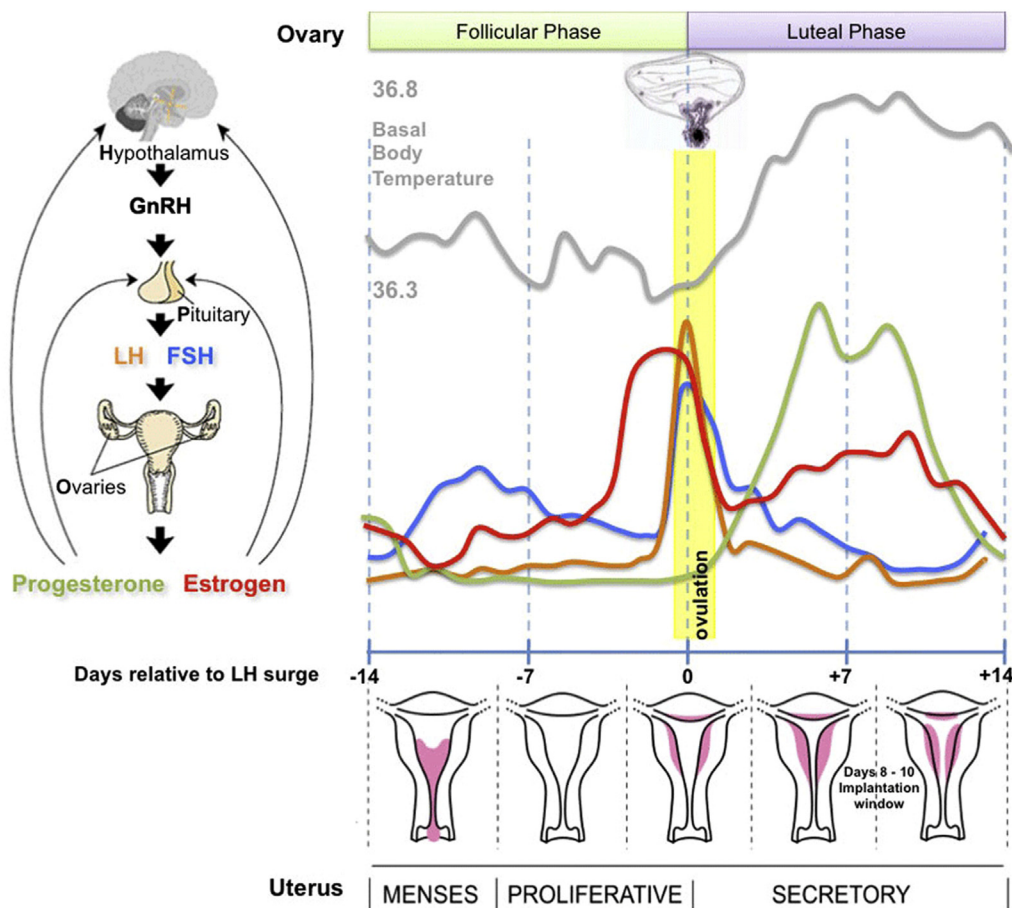


Figure 1. Menstrual cycle. FSH, Follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone. Reproduced from Buchheit et al¹⁷ with permission.

estrogen hypersensitivity, catamenial anaphylaxis, or lactation-associated anaphylaxis. Although believed to be rare, each of these disease entities has been well documented in the medical literature. Of these conditions, PH is the most common. Therefore, this review will discuss the clinical presentation, diagnosis, treatment, and proposed pathomechanisms of various causes of cyclical hypersensitivity or anaphylaxis with a primary focus on PH.

Epidemiology

Cyclical hypersensitivity is relatively rare, with fewer than 200 total reported cases. It is likely underdiagnosed, and there are currently no published epidemiologic data that quantify incidence or prevalence. Women of child-bearing age are predominantly affected, with symptom onset starting between menarche and menopause. A review of 89 published cases and a large case series with 24 patients revealed a mean age at onset of 27.3 years (range, 12–47 years) and 29.7 years (range, 13–48 years), respectively.^{1,2} There is one published case report of a male with hypersensitivity manifested by generalized, pruritic, erythematous, morbilliform, scaling dermatitis to megestrol acetate, a synthetic orally active form of progesterone used to stimulate appetite and weight gain in cachectic patients.³

In addition to being a reproductive-age female, having current or prior exogenous progesterone exposure appears to be a risk factor,² although there are many case reports in patients who experience symptoms without prior exogenous progesterone exposure, which only correlated with endogenous progesterone exposure during menses or pregnancy.^{4,5} Of note, cyclical hypersensitivities have not been reported in postmenopausal women undergoing hormone replacement therapy.

Menstrual Cycle Physiology

Progesterone is an endogenous steroid-derived sex hormone that plays critical roles in the female menstrual cycle, pregnancy, lactation, and human embryogenesis. In addition to its roles in reproductive physiology, it has anti-inflammatory properties and plays a role in T-lymphocyte-mediated immune responses.⁶ During the menstrual cycle, the ovarian corpus luteum secretes progesterone during the luteal phase, which prepares the uterine endometrial lining for ovum implantation and subsequent pregnancy. Progesterone levels start to increase approximately 24 to 48 hours before ovulation and peak at approximately days 20 to 21 of a 28-day cycle (Fig. 1). If no implantation occurs, progesterone levels decrease and the endometrial lining sloughs, resulting in menstruation. If implantation occurs, progesterone levels remain elevated, and the maternal immune response is dampened to help allow for embryogenesis. During pregnancy, progesterone also relaxes uterine smooth muscle contractility and inhibits lactation. Eventually, progesterone levels decrease to precipitate labor and induce lactation.^{6–8}

Catamenial Hypersensitivity

Dermatoses and anaphylaxis in temporal association with the menstrual cycle have been reported.^{9–12} Catamenial anaphylaxis correlates with onset of menstrual cycle when progesterone and estrogen levels begin to decrease after menses onset. This is in contrast to symptoms of progestogen hypersensitivity, which occur at peak concentration of progesterone, which occurs before onset of menses.¹³ The term *catamenial anaphylaxis* has also been used in the literature to describe premenstrual responses to progesterone.^{9,11} One suggested pathomechanism is that the hypersensitivity

reaction is triggered by release of prostaglandins from the endometrium, which peaks on the first day of the menstrual cycle. It is thought that progesterone F₂ synthesized by the endometrium mediates uterine mast cell activation and release of bioactive mediators, leading to clinical symptoms.^{10,12,14} Successful treatment for catamenial hypersensitivity has been achieved in some cases with nonsteroidal anti-inflammatory agents such as indomethacin, which inhibit prostaglandins, and by hysterectomy with bilateral salpingo-oophorectomy.¹⁰

Progestogen Hypersensitivity

PH, a form of catamenial anaphylaxis, manifests clinically with cutaneous and noncutaneous signs and symptoms. Patients usually present with localized cutaneous or systemic symptoms, although a given patient's reaction may evolve with time and vary from month to month. Patients can present with multiple cutaneous reactions,¹⁵ including maculopapular rash, papules and plaques,^{16,17} eczematous dermatitis,^{18,19} urticaria with or without angioedema,^{20–25} vesiculobullous and/or vesiculopustular lesions,^{7,16} petechiae and purpura,^{5,26} stomatitis,^{27,28} vulvovaginal pruritus,²⁹ erythema multiforme,^{30,31} fixed drug eruption,^{32,33} or Stevens-Johnson syndrome.^{34,35} In each of these cases, PH was confirmed through positive progesterone skin testing (immediate epicutaneous and intracutaneous testing, delayed intracutaneous testing response, or patch testing), a progesterone challenge that provoked symptoms or clear improvement with treatment, which are discussed below.

As mentioned, some patients with PD present with systemic reactions. Bernstein et al³⁶ reported a detailed case of a 26-year-old woman on an estrogen-progestin oral contraceptive to manage oligomenorrhea and polycystic ovarian syndrome who subsequently developed anaphylaxis manifested by lip and facial angioedema, bronchospasm, and hypotension within 48 hours of starting the contraceptive. Use of the contraceptive was discontinued. Two weeks later, use was restarted with a similar reaction, followed by 3 additional episodes of anaphylaxis of increasing severity while she continued to take the contraceptive. Years later, the same patient developed maculopapular dermatitis on her face and neck that occurred cyclically with her menstrual cycle. She responded to an oral gonadotropin-releasing hormone (GnRH) agonist and subsequently to an intranasal GnRH agonist preparation. Of note, her symptoms resolved after menopause many years later. In contrast, a 24-patient case series of PH reported that 13% had symptoms of asthma, which correlated with exogenous estrogen exposure or menstrual cycle.¹

Symptom onset can be at any time point from menarche to menopause, without a clear inciting event. Some patients have had onset of symptoms after completion of an uneventful pregnancy. For women exposed to exogenous progestogens, symptoms may start any time after first exposure and have been reported to be triggered by exogenous progestogens alone or in conjunction with a surge in progesterone during the menstrual cycle.

Timing of symptoms differs with disease caused by endogenous or exogenous progestogens. For reactions to endogenous progesterone, the cyclical nature of reaction in association with the menstrual cycle is an important diagnostic criterion. Signs and symptoms occur during times with peak progesterone levels of the luteal phase, which typically occurs 3 to 10 days before menses onset.^{1,2} Although symptoms may persist throughout the entire menstrual cycle, they frequently resolve after a few days of menstruation but can persist through the cycle. Cyclical patterns can be challenging to detect in women with irregular menstrual cycles, particularly because of difficulty in establishing a correlation between symptoms and progesterone surge. Cycles that are greater than 45 days tend to be anovulatory or oligo-ovulatory and thus are unlikely to have the progesterone surge that elicits PH. Thus, other causes should be considered in such

patients.²⁰ For exogenous progestin exposure, reactions typically correlate with administration of exogenous progestogens, and thus there is often no association with the menstrual cycle.

Estrogen Hypersensitivity

Endogenous and exogenous estrogen hypersensitivity reactions, also a form of catamenial hypersensitivity, have been described in multiple case reports and case series.^{37–42} The typical presentation involves a premenstrual flare of urticaria or delayed-type dermatitis, consistent with its reference in the literature as “estrogen dermatitis.”³⁸ Estrogen hypersensitivity can be confirmed by positive immediate or sometimes by delayed intracutaneous testing.^{38,39} Another diagnostic approach is a positive estrogen challenge result.³⁷ The pathomechanism is not fully understood, but an allergic mechanism mediated by dendritic cells has been proposed.⁴⁰ Successful treatment has been demonstrated with suppression of estrogen with estrogen modulators, such as leuprolide acetate⁴¹ or tamoxifen.^{38,39} Other effective approaches include progestin-only contraceptive⁴² or oophorectomy.³⁷ Patients who are symptomatic because of exogenous estrogen exposure have been able to mitigate symptoms by stopping estrogen therapy.³⁸

Lactation-Associated Hypersensitivity

A number of cases that involve lactation-associated anaphylaxis have been reported.^{43–48} The cases are typically associated with manual expression of breast milk or the act of breastfeeding, usually in the first few days after delivery. Elevated serum tryptase levels have been reported with breastfeeding-associated anaphylaxis.⁴⁸ Although this condition is not a true form of cyclical anaphylaxis, it is believed to be regulated by changes in progesterone levels during and after labor. The proposed mechanism has been postulated to involve progesterone stabilization of mast cell membranes during pregnancy and further stabilization during labor because of increased cortisol release followed by a postpartum decrease in hormones essential for lactogenesis, leading to an exaggerated histamine response.⁴³ An alternative theory is that postpartum nonsteroidal anti-inflammatory drugs, often given for pain control, may be the trigger for anaphylaxis.^{43,46,47} Finally, hypersensitivity to hormones involved in breast milk production and excretion are also considerations. However, skin testing to prolactin and oxytocin

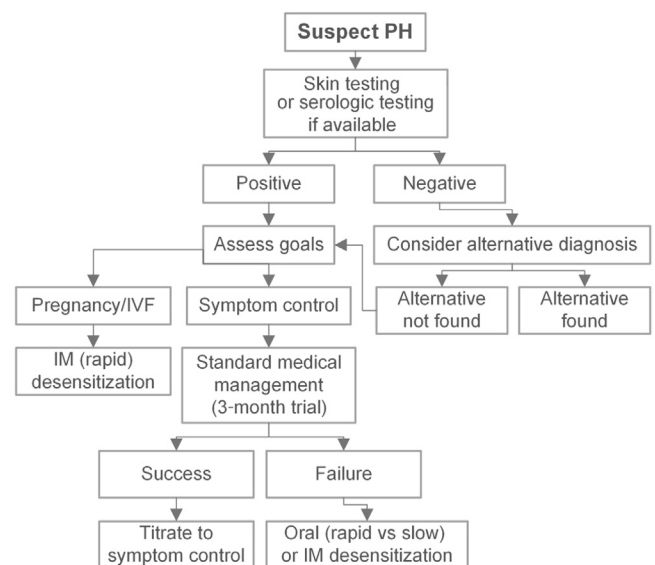


Figure 2. Algorithmic approach for diagnosis and treatment of progestogen hypersensitivity. IM, intramuscular; IVF, in vitro fertilization; PH, progestogen hypersensitivity. Reproduced from Foer et al¹ with permission.

produced negative results.^{43,46} In some cases, lactation-associated hypersensitivity or anaphylaxis have occurred with subsequent pregnancies.^{45,46} Although these cases could also represent idiopathic anaphylaxis, in several cases, symptoms resolve after a few days of breastfeeding.⁴⁶ When symptoms do not resolve, pharmacologic suppression of lactation with a medication such as bromocriptine has been reported to be a useful strategy.^{43,45}

Etiology and Potential Pathogenesis for Cyclical Hypersensitivities

Because cyclical hypersensitivities have diverse clinical manifestations, multiple mechanisms are likely involved that vary among patients. Most cases of cyclical hypersensitivity are secondary to PH, such as exposure to exogenous progestins or endogenous progesterone. Exogenous progestin exposure is often through contraceptive pharmaceuticals, including oral contraceptive pills,^{7,18,36} depot medroxyprogesterone,^{20,49} or progestin-containing intrauterine devices¹ or vaginal rings.⁵⁰ In addition, high-dose progesterone exposure during emergency contraception or in vitro fertilization has been associated with PH.^{1,18} Endogenous progesterone is secreted during the luteal phase of the menstrual cycle by the corpus luteum.²⁰ In the event of pregnancy, endogenous progesterone is initially secreted by the corpus luteum and then by the placenta once formed.^{50,51}

Most forms of PH are thought to be an immediate-type (type I) hypersensitivity. In this circumstance, the body forms progesterone specific IgE, typically after exposure to exogenous progestogens, such as synthetic progestins used in contraception or exogenous progesterone. It is plausible that exogenous progestins could be recognized as foreign by the immune system because they are derived from modifying side chains of 19-nortestosterone, 17- α -hydroxyprogesterone or 17-acetoxypregesterone. These may be sufficiently different from endogenous progesterone to invoke antibody production against a perceived foreign threat. Once the body has formed progesterone specific IgE, subsequent exposure may

elicit an immediate reaction by cross-linking of IgE antibodies on surface of mast cells and/or basophils, with subsequent degranulation and mediator release.^{1,24,25} Positive skin test results (discussed below) have been found in many cases of PH, which provides supporting evidence of an immediate hypersensitivity mechanism.^{25,52} Further evidence of an immediate hypersensitivity mechanism is found using functional assays of mast cell and basophil activation.^{19,53} Some patients have a reaction history but negative skin prick test results to progesterone. In this case, a putative mechanism may be direct progesterone-induced mast cell or basophil activation with subsequent release of mediators. Although mast cells express progesterone and estradiol receptors, the direct activating effect by hormones on mast cells has not been well studied.^{54–56}

It is also hypothesized that some PH reactions are mediated through a delayed-type (type IV), T-lymphocyte-mediated hypersensitivity, which may in part explain the vesicular eruptions experienced by our patient. Evidence of delayed-type hypersensitivity is supported by delayed reactions to progesterone skin prick or intracutaneous testing by some patients.^{51,57,58} This mechanism is additionally supported by a study in which 5 of 19 patients with contact dermatitis to hydrocortisone had positive patch test result to 17- α -progesterone. In this study, the authors postulated that cross-sensitization to progesterone may result from primary sensitization with structurally similar corticosteroids. Notably, only 2 of 5 patch test–positive patients had a clinical reaction consistent with PH.⁵⁹ Furthermore, reactions from topical and oral corticosteroids are not typically found in patients with PH, and corticosteroids are commonly used to treat PH. Severe reactions linked to progestogen exposure that are consistent with cyclical Stevens-Johnson syndrome have also been described, which provides further evidence for a cell-mediated process.^{34,35}

Lastly, the existence of progesterone specific IgG antibodies with subsequent immune complex formation and tissue deposition (type III hypersensitivity) has been proposed as a mechanism for PH. A patient with cyclical development of oral and perineal rashes had

A			
Day	Dose (based on progestion component)	No. of capsules $\times$ capsule dose per day	Total daily dose
1	1.25 μ g in AM, 2.5 μ g in PM	1 $\times$ 1.25 μ g; 2 $\times$ 1.25 μ g	3.75 μ g
2	2.5 μ g in AM, 12.5 μ g in PM	2 $\times$ 1.25 μ g; 1 $\times$ 12.5 μ g	15 μ g
3	12.5 μ g in AM, 2.5 μ g in PM	1 $\times$ 12.5 μ g; 2 $\times$ 12.5 μ g	37.5 μ g
4	37.5 μ g in AM, 12.5 μ g in PM	3 $\times$ 12.5 μ g; 3 $\times$ 12.5 μ g	75 μ g
5	50 μ g in AM, 2.5 μ g in PM	1 $\times$ 50 μ g; 1 $\times$ 50 μ g; 2 $\times$ 12.5 μ g	125 μ g
6	250 μ g	2 $\times$ 125 μ g	250 μ g
7	500 μ g	4 $\times$ 125 μ g	500 μ g
8	500 μ g	4 $\times$ 125 μ g	500 μ g
9	1 mg	1 $\times$ 1 mg	1 mg
Target dose for this period. Norethindrone 1 mg/ethinyl estradiol 0.02 mg.			
B		C	
Time h	Dose	Time	Dose of IM progesterone 50 mg/mL
00:00 (first day)	0.1 mg	0 min	1 mg
00:45	1 mg	30 min	2 mg
01:30	5 mg	60 min	4 mg
02:15	10 mg	90 min	8 mg
03:00	25 mg	120 min	16 mg
00:00 (next day)	50 mg	150 min	18.5 mg
00:45	100 mg	Total dose	50 mg
01:30	100 mg	Target daily dose	Intravaginal/Progesterone 90–180 mg (ie, 8% gel once or twice daily) or IM progesterone 50–75 mg daily, depending on IVF protocol

Figure 3. Desensitization protocols for intramuscular and oral progestins. A, Gradual oral protocol; B, 2-day oral protocol; C, rapid intramuscular (IM) protocol. IVF, in vitro fertilization. Reproduced from Buchheit et al¹⁷ with permission.

circulating IgG to 17-hydroxyprogesterone.⁶⁰ Another case described a patient with cyclical erythema multiforme during luteal phase of her menstrual cycle who developed cutaneous IgG immune complex deposition after provocation with medroxyprogesterone.³⁰ However, presence of antiprogestosterone IgG has not been well characterized, and it is possible that many asymptomatic individuals have this circulating antibody without clinical manifestation of PH.

Diagnostic Evaluation

Diagnostic evaluation of cyclical hypersensitivity or anaphylaxis starts with a thorough history, particularly focusing on signs and symptoms of hypersensitivity that correlate with the luteal phase of the menstrual cycle or with exposure to exogenous sex hormones. Skin findings are common, including urticaria, angioedema, eczema, pruritus, vesicular, bullous or pustular lesions, petechiae or purpura, stomatitis, or erythema multiforme. Furthermore, patients may present with respiratory distress, wheeze, or frank anaphylaxis. In addition, history should consider other possible culprits that have a temporal association with the luteal phase, such as premenstrual use of nonsteroidal anti-inflammatory drugs. Other disease entities that may explain symptoms must be excluded, including idiopathic urticaria, allergic contact dermatitis, or atopic dermatitis. If a high index of suspicion exists for PH, the diagnosis can be confirmed with progesterone skin testing, progesterone challenge, or in vitro assays.

Skin prick and intracutaneous testing with progesterone have been used to confirm PH^{25,61} both for delayed^{57,58,62} and immediate^{1,63} progestogen hypersensitivities (Fig. 2). Because progesterone skin testing is not standardized, some investigators have used concentration pharmaceutical grade progesterone (50 mg/mL) for skin prick testing, whereas others have used a bioidentical progesterone compounded with olive oil or benzyl alcohol because progesterone is not water soluble. If skin prick test results are negative, intracutaneous testing is then performed, with dilutions starting at a 0.05-mg/mL solution and increasing stepwise if negative with 0.5- and 5-mg/mL solutions. The use of injectable formulations, such as medroxyprogesterone for skin testing at an intracutaneous dilutional concentration ranging from 1.5 to 10 mg/mL (.03 mL) also suspended in oils, has been used but may cause an irritant response.⁹ Others have reported using medroxyprogesterone diluted in phenol saline up to a maximum of 2 mg in a volume of 20 μ L.⁶⁴ An irritant response or large local reaction is not considered diagnostic of PH. Typically, a positive skin test result is considered a wheal 3 mm or larger with concomitant erythema in the presence of a positive histamine and negative saline control similar to standard allergen testing. It is advised to also test negative controls to ensure that test results are not irritant induced.^{1,25,62} The positive and negative predictive values of skin testing with synthetic progestins is unknown because of a lack of standardization. Furthermore, although positive skin test results

can lead to confirmation of the diagnosis, negative skin test results do not rule out hypersensitivity. In addition, patch testing with progesterone has been attempted, but there is no evidence that it confers diagnostic yield.⁶⁵ Finally, patient serum samples collected during follicular and luteal phases of the menstrual cycle have been used for autologous serum skin testing to confirm a diagnosis.⁶¹

Another useful diagnostic modality is progesterone challenge. However, this approach must be considered carefully because, although provocation of symptoms with progesterone challenge can be useful to confirm a questionable diagnosis, it can also cause exacerbate existing severe dermatitis,³⁰ leading to unnecessary morbidity. Therefore, alternative approaches should be considered, including skin testing, empiric treatment of symptoms,^{50,66} or desensitization.^{21,24}

Experimental in vitro tests have been described that may diagnose or confirm PH. Bernstein et al³⁶ described the first report of combined recurrent anaphylaxis with cyclical urticaria and angioedema. For this assay, an enzyme-linked immunosorbent assay was performed using polystyrene microtiter plates coated with progesterone-bovine serum albumin-conjugated antigen, which were incubated in a stepwise fashion with antihuman goat IgE or IgG, anti-goat IgE, or IgG alkaline phosphatase, followed by substrate p-nitrophenol phosphate (Ghosh D, Bernstein JA, submitted to Annals Allergy Asthma Clin Immunol 2018). The results of a direct leukocyte histamine release assay on basophils from this patient were persistently positive to 5-pregnandiol. The results were also inhibited by antiprogestosterone mouse monoclonal antibody and progesterone inhibitor mifepristone. In addition, enzyme-linked immunosorbent assay, one of the most reliable methods to identify IgE-mediated immune response, indicated that the patient had IgE specific to progesterone. Confirmation of progesterone sensitivity using an interferon γ release assay to establish drug-related T-cell activity has also been demonstrated.⁶⁷

Treatment

Progestogen and estrogen hypersensitivity treatment approaches are tailored to each individual's symptoms and therapeutic goals. Treatment approaches often involve collaboration between multiple practitioners, including a patient's allergist/immunologist, dermatologist, and/or gynecologist, depending on the specific goals of the patient (Fig. 2).

Avoiding the offending agent, particularly in the case of exogenous progestogens, is the simplest approach to managing PH. Symptomatic control is a starting point if progesterone is endogenous and/or necessary for the patient. In some cases, suppression of ovulation may be a recommendation.

Relief of urticaria, angioedema, and pruritus can be achieved through oral antihistamines,^{15,21,68} preferably nonsedating or low-sedating H₁-antagonists, which are usually better tolerated than the first-generation, more sedating H₁-antagonists. Some patients may require a higher than usual starting dose because symptomatic relief has a varying effect, depending on the patient. Response to mediator

Table 1
Treatment Options in Progestogen Hypersensitivity

Treatment category	Drug class	Potential problems
Symptomatic relief	Oral antihistamines	Incomplete efficacy
	Topical glucocorticoids	Incomplete efficacy
Ovulation suppression	Systemic glucocorticoids	Incomplete efficacy, long-term adverse effects
	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

Abbreviations: GnRH, gonadotropin-releasing hormone; IM, intramuscular; LFT, liver function test. Reproduced from Buchheit et al¹⁷ with permission.

blockers should be realized within 2 to 4 weeks if they are to be effective. Topical or systemic glucocorticoids can also be helpful, but their prolonged use is associated with many unfavorable adverse effects, making them less desirable as a prophylactic treatment.^{18,60}

Suppression of ovulation can be achieved by combined oral contraceptive pills, but this is often poorly tolerated because they often contain both progesterone and estrogen.⁴⁹ Tolerance may be improved by giving an oral contraceptive with a constant progesterone dose and giving this same dose continuously. This approach is contraindicated in patients with anaphylaxis or a history of blistering lesions of the skin or mucous membranes. If oral contraceptive pills are not well tolerated, desensitization may be a useful strategy.¹ Although desensitization is not a cure for drug hypersensitivity, it is a well-established means for curtailing symptoms as long as the patient continues to take the drug. This approach can be particularly useful for patients who will be taking progesterone only (such as oral contraceptives) or a patient who will require only a limited time frame of exposure (such as during fertility treatment). Multiple desensitization protocols (Fig. 3) have been used for symptomatic relief of a variety of symptoms in patients with PH.^{1,21,24} Indications for desensitization include a severe symptoms not controlled with standard therapy (H₁-antagonists and/or glucocorticoids) and/or the requirement for high-dose progesterone for fertility treatment (in vitro fertilization).^{21,24} To ensure patient safety, desensitization protocols are best performed by allergists or other practitioners with specific training in desensitization procedures, particularly for patients with progesterone-induced urticaria, asthma, or anaphylaxis. If symptoms develop during the desensitization protocol, it may be necessary to temporarily stop or modify the protocol to successfully complete the process.

For immediate reactions, rapid desensitization protocols can be achieved in a matter of hours.^{69–71} For delayed reactions, protocols that involve gradual dose escalation may be used.¹ Some experts prefer to give patients diphenhydramine (50 mg orally) and prednisone (40 mg orally for 3 days) as premedications before initiation of rapid drug desensitization protocols. If patients develop symptoms during the protocol, the protocol can be adjusted by backing up to the last tolerated dose and progressing more gradually through subsequent steps.

Omalizumab had efficacy in a young woman with urticaria and anaphylaxis caused by PH.⁵² Although omalizumab is usually well tolerated and has few adverse effects, it is likely only effective as long as it is regularly administered. It is unclear whether the treatment response was directly attributable to omalizumab or the actual desensitization to progesterone, which alleviated the allergic symptoms and nonallergic vesicular eruptions experienced by this patient. It is plausible that the omalizumab simply controlled the IgE-mediated clinical symptoms, making desensitization possible. Because both treatments were being administered simultaneously, it is not possible to discern their individual clinical responses. Further investigation in the pathomechanisms of PH is required to explain this clinical response.

A treatment paradigm can be tailored to the woman's future pregnancy plans, including different approaches for women with a desire to conceive, women participating in fertility treatments, women who do not desire pregnancy in the near future, and women who are finished with childbearing. For women with the desire to conceive, symptomatic management with antihistamines and glucocorticoids is a good starting point. These patients can conceive naturally with the hope that they will achieve an endogenous autodesensitization as a direct consequence of pregnancy. There are no data that PH is a cause of infertility. Use of omalizumab may be a good adjunctive therapy in patients with urticaria, asthma, or anaphylaxis. Women who are undergoing infertility treatments with PH typically require desensitization to tolerate the

high doses of progesterone necessary for embryo implantation. These patients may benefit from the rapid-dose escalation protocols as a bridge to tolerating the high progesterone dose. Various published protocols use oral, intravaginal, or intramuscular progesterone.^{1,21,24,25} Desensitization can be timed to be shortly performed before embryo transfer. Collaboration with the reproductive endocrinologist is imperative.

Women who do not desire pregnancy in the near future may benefit from the use of oral contraceptives that contain both progestins and estrogen to eliminate the progesterone peaks that initiate reactions. Starting use of oral contraceptives with usual dosing is often not tolerated in patients with a history of PH. Thus, therapy can be initiated with a slow oral protocol. This approach is best tolerated with preparations that combine estrogen with a constant dose of progestin given continuously throughout the cycle without stopping to allow for menses; otherwise, patients may experience resensitization.

For women who are finished with childbearing, alternatives exist to rapid desensitization followed by continuous estrogen- and progesterone-containing oral contraceptives until menopause. However, these options, which include GnRH agonists, tamoxifen, and oophorectomy, have significant disadvantages. In patients with severe signs and symptoms that are refractory to other therapies, successful treatment has occurred with GnRH agonists, such as leuprolide acetate.^{36,49,68} Doses that suppress ovulation work by inhibiting release of pituitary gonadotropins with resultant inhibition of ovulation and luteal progesterone suppression.⁷² A double-blind, crossover study was performed in 4 women with a history of cyclical anaphylaxis during the luteal phase. All received a placebo or a GnRH agonist. Two of the 4 patients improved while taking a GnRH agonist, whereas the other 2 had no response. The 2 who demonstrated improvement had positive skin test results to medroxyprogesterone acetate. Furthermore, they experienced anaphylaxis to intravenous provocation with luteinizing hormone-releasing hormone, consistent with PH.⁶⁴ The intranasal GnRH agonist nafarelin has been used to control symptoms in a patient with PH as previously mentioned.³⁰ The selective estrogen receptor modulator drug tamoxifen, as well as danazol or stanozolol, which are 17- α -alkylated steroids, have also been reported as helpful in treating PH.^{27,30,73} In premenopausal women, tamoxifen induces ovulation. However, if given as regular, daily doses, it will induce an oligomenorrheic or amenorrheic state. Higher risk of thromboembolic events, hot flashes, and abnormal uterine bleeding are among its adverse effects. Finally, oophorectomy has been used as definitive therapy for patients with severe PH that is refractory to other approaches.^{4,28,66,74} A trial with a GnRH agonist before oophorectomy can be helpful to confirm symptomatic improvement on suppression of endogenous progesterone. If oophorectomy is chosen as the treatment option, these women should be counseled about the need to use supplemental estrogen postsurgically to avoid complications caused by postmenopausal-induced estrogen deficiency, such as osteopenia or osteoporosis. Table 1 summarizes the treatment options.

Conclusion

Multiple syndromes are associated with cyclical hypersensitivity and anaphylaxis, all of which are tied to the physiologic mechanisms of the female reproductive system. The most commonly reported cause of cyclical hypersensitivity and anaphylaxis is progesterone, but estrogen exposure, catamenial anaphylaxis, and lactation-associated anaphylaxis are also well-described cyclical hypersensitivities. Swift recognition of these syndromes with a thoughtful diagnostic approach and collaborative efforts with the patient's gynecologist and an allergist/clinical immunologist can help ensure timely and effective treatment outcomes.

References

1. Foer D, Buchheit KM, Gargiulo AR, Lynch DM, Castells M, Wickner PG. Progesterone hypersensitivity in 24 cases: diagnosis, management, and proposed renaming and classification. *J Allergy Clin Immunol Pract*. 2016;4:723–729.
2. Nguyen T, Razzaque A. Autoimmune progesterone dermatitis: update and insights. *Autoimmun Rev*. 2016;15:191–197.
3. Fisher DA. Drug-induced progesterone dermatitis. *J Am Acad Dermatol*. 1996;34:863–864.
4. Moody BR, Schatten S. Autoimmune progesterone dermatitis: onset in a woman without previous exogenous progesterone exposure. *South Med J*. 1997;90:845–846.
5. Wintzen M, Goor-van Egmond MB, Noz KC. Autoimmune progesterone dermatitis presenting with purpura and petechiae. *Clin Exp Dermatol*. 2004;29:316.
6. Taraborrelli S. Physiology, production and action of progesterone. *Acta Obstet Gynecol Scand*. 2015;94(suppl 161):8–16.
7. Hart R. Autoimmune progesterone dermatitis. *Arch Dermatol*. 1977;113:426–430.
8. Forbes TR. Systemic plasma progesterone levels during the human menstrual cycle. *Am J Obstet Gynecol*. 1950;60:180–186.
9. Bauer CS, Kampitak T, Messieh ML, Kelly KJ, Vadas P. Heterogeneity in presentation and treatment of catamenial anaphylaxis. *Ann Allergy Asthma Immunol*. 2013;111:107–111.
10. Burstein M, Rubinow A, Shalit M. Cyclic anaphylaxis associated with menstruation. *Ann Allergy*. 1991;66:36–38.
11. Lieberman P. Catamenial anaphylaxis. *J Allergy Clin Immunol Pract*. 2014;2:358–359.
12. Verdolini R, Atkar R, Clayton N, Hasan R, Stefanato CM. Catamenial dermatoses: has anyone ever considered prostaglandins? *Clin Exp Dermatol*. 2014;39:509–512.
13. Snyder JL, Krishnaswamy G. Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review. *Ann Allergy Asthma Immunol*. 2003;90:469–477. quiz 477, 571.
14. Singh EJ, Baccarini I, Zuspan FP. Levels of prostaglandins F-2alpha and E-2 in human endometrium during the menstrual cycle. *Am J Obstet Gynecol*. 1975;121:1003–1006.
15. Walling HW, Scupham RK. Autoimmune progesterone dermatitis: case report with histologic overlap of erythema multiforme and urticaria. *Int J Dermatol*. 2008;47:380–382.
16. Herzberg AJ, Strohmeier CR, Cirillo-Hyland VA. Autoimmune progesterone dermatitis. *J Am Acad Dermatol*. 1995;32:333–338.
17. Buchheit KM, Bernstein JA. Progesterone hypersensitivity: heterogeneous manifestations with a common trigger. *J Allergy Clin Immunol Pract*. 2017;5:566–574.
18. Jenkins J, Geng A, Robinson-Bostom L. Autoimmune progesterone dermatitis associated with infertility treatment. *J Am Acad Dermatol*. 2008;58:353–355.
19. Jones WN, Gordon VH. Auto-immune progesterone eczema: an endogenous progesterone hypersensitivity. *Arch Dermatol*. 1969;99:57–59.
20. Baptist AP, Baldwin JL. Autoimmune progesterone dermatitis in a patient with endometriosis: case report and review of the literature. *Clin Mol Allergy*. 2004;2:10.
21. Poole JA, Rosenwasser LJ. Chronic idiopathic urticaria exacerbated with progesterone therapy treated with novel desensitization protocol. *J Allergy Clin Immunol*. 2004;114:456–457.
22. Farah FS, Shbaklu Z. Autoimmune progesterone urticaria. *J Allergy Clin Immunol*. 1971;48:257–261.
23. Vasconcelos C, Xavier P, Viera AP, et al. Autoimmune progesterone urticaria. *Gynecol Endocrinol*. 2000;14:245–247.
24. Prieto-Garcia A, Sloane DE, Gargiulo AR, Feldweg AM, Castells M. Autoimmune progesterone dermatitis: clinical presentation and management with progesterone desensitization for successful in vitro fertilization. *Fertil Steril*. 2011;95:1121.e9–13.
25. Hill JL, Carr TF. Iatrogenic autoimmune progesterone dermatitis treated with a novel intramuscular progesterone desensitization protocol. *J Allergy Clin Immunol Pract*. 2013;1:537–538.
26. Mbonile L. Autoimmune progesterone dermatitis: Case report with history of urticaria, petechiae and palpable pinpoint purpura triggered by medical abortion. *S Afr Med J*. 2016;106:48–50.
27. Moghadam BK, Hersini S, Barker BF. Autoimmune progesterone dermatitis and stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85:537–541.
28. Berger H. Progesterone. *Arch Dermatol*. 1969;100:117.
29. Banerjee AK, de Chazal R. Chronic vulvovaginal pruritus treated successfully with GnRH analogue. *Postgrad Med J*. 2006;82:e22.
30. Wojnarowska F, Greaves MW, Peachey RD, Drury PL, Besser GM. Progesterone-induced erythema multiforme. *J R Soc Med*. 1985;78:407–408.
31. Maguire T. Autoimmune progesterone dermatitis. *Dermatol Nurs*. 2009;21:190–192.
32. Asai J, Katoh N, Nakano M, Wada M, Kishimoto S. Case of autoimmune progesterone dermatitis presenting as fixed drug eruption. *J Dermatol*. 2009;36:643–645.
33. Honda T, Kabashima K, Fujii Y, Katoh M, Miyachi Y. Autoimmune progesterone dermatitis that changed its clinical manifestation from anaphylaxis to fixed drug eruption-like erythema. *J Dermatol*. 2014;41:447–448.
34. Drayer SM, Laufer LR, Farrell ME. Autoimmune progesterone dermatitis presenting as Stevens-Johnson syndrome. *Obstet Gynecol*. 2017;130:881–884.
35. Drayer SM, Laufer LR, Farrell ME. Autoimmune progesterone dermatitis mistaken for Stevens-Johnson syndrome. *Obstet Gynecol*. 2018;131:723–726.
36. Bernstein IL, Bernstein DI, Lummus Z, Bernstein JA. A case of progesterone-induced anaphylaxis, cyclic urticaria/angioedema, and autoimmune dermatitis. *J Womens Health (Larchmt)*. 2011;20:643–648.
37. Mayou SC, Charles-Holmes R, Kenney A, Black MM. A premenstrual urticarial eruption treated with bilateral oophorectomy and hysterectomy. *Clin Exp Dermatol*. 1988;13:114–116.
38. Shelley WB, Shelley ED, Talanin NY, Santoso-Pham J. Estrogen dermatitis. *J Am Acad Dermatol*. 1995;32:25–31.
39. Leylek OA, Unlü S, Öztürkcan S, Cetin A, Sahin M, Yildiz E. Estrogen dermatitis. *Eur J Obstet Gynecol Reprod Biol*. 1997;72:97–103.
40. Yotsumoto S, Shimomai K, Hashiguchi T, et al. Estrogen dermatitis: a dendritic-cell-mediated allergic condition. *Dermatology*. 2003;207:265–268.
41. Yoon TY, Kim YG, Kim K. Estrogen dermatitis responding to leuprolide acetate. *J Dermatol*. 2005;32:405–406.
42. Randall K, Steele R. Estrogen dermatitis: treatment with progestin-only pill. *Arch Dermatol*. 2005;141:792–793.
43. Mullins RJ, Russell A, McGrath GJ, Smith R, Sutherland DC. Breastfeeding anaphylaxis. *Lancet*. 1991;338:1279–1280.
44. MacDonell JW, Ito S. Breastfeeding anaphylaxis case study. *J Hum Lact*. 1998;14:243–244.
45. Villalta D, Martelli P. A case of breastfeeding anaphylaxis. *Eur Ann Allergy Clin Immunol*. 2007;39:26–27.
46. Shank JJ, Olney SC, Lin FL, McNamara MF. Recurrent postpartum anaphylaxis with breast-feeding. *Obstet Gynecol*. 2009;114:415–416.
47. McKinney KK, Scranton SE. A case report of breastfeeding anaphylaxis: successful prophylaxis with oral antihistamines. *Allergy*. 2011;66:435–436.
48. Durgakeri P, Jones B. A rare case of lactation anaphylaxis. *Australas Med J*. 2015;8:103–105.
49. Toms-Whittle LM, John LH, Griffiths DJ, Buckley DA. Autoimmune progesterone dermatitis: a diagnosis easily missed. *Clin Exp Dermatol*. 2011;36:378–380.
50. Camoes S, Sampaio J, Rocha J, Tiago P, Lopes C. Autoimmune progesterone dermatitis: case report of an unexpected treatment reaction. *Australas J Dermatol*. 2017;58:e132–e134.
51. Georgouras K. Autoimmune progesterone dermatitis. *Australas J Dermatol*. 1981;22:109–112.
52. Heffler E, Fichera S, Nicolosi G, Crimi N. Anaphylaxis due to progesterone hypersensitivity successfully treated with omalizumab. *J Allergy Clin Immunol Pract*. 2017;5:852–854.
53. Miura T, Matsuda M, Yanbe H, Sugiyama S. Two cases of autoimmune progesterone dermatitis. Immunohistochemical and serological studies. *Acta Derm Venereol*. 1989;69:308–310.
54. Slater JE, Kaliner M. Effects of sex hormones on basophil histamine release in recurrent idiopathic anaphylaxis. *J Allergy Clin Immunol*. 1987;80:285–290.
55. Zaitis M, Narita S, Lambert KC, et al. Estradiol activates mast cells via a non-genomic estrogen receptor-alpha and calcium influx. *Mol Immunol*. 2007;44:1977–1985.
56. Zierau O, Zenclussen AC, Jensen F. Role of female sex hormones, estradiol and progesterone, in mast cell behavior. *Front Immunol*. 2012;3:169.
57. Chawla SV, Quirk C, Sondheimer SJ, James WD. Autoimmune progesterone dermatitis. *Arch Dermatol*. 2009;145:341–342.
58. Teelucksingh S, Edwards CR. Autoimmune progesterone dermatitis. *J Intern Med*. 1990;227:143–144.
59. Schoenmakers A, Vermorken A, Degreef H, Dooms-Goossens A. Corticosteroid or steroid allergy? *Contact Dermatitis*. 1992;26:159–162.
60. Cheesman KL, Gaynor LV, Chatterton RT Jr, Radvany RM. Identification of a 17-hydroxyprogesterone-binding immunoglobulin in the serum of a woman with periodic rashes. *J Clin Endocrinol Metab*. 1982;55:597–599.
61. Garcia-Ortega P, Scorza E. Progesterone autoimmune dermatitis with positive autologous serum skin test result. *Obstet Gynecol*. 2011;117:495–498.
62. Baer RL, Witten VH, Allen JR. Skin tests with endocrine substances; method of Zondek and Bromberg. *Ann Allergy*. 1948;6:239–251.
63. Lee MK, Lee WY, Yong SJ, et al. A case of autoimmune progesterone dermatitis misdiagnosed as allergic contact dermatitis. *Allergy Asthma Immunol Res*. 2011;3:141–144.
64. Slater JE, Raphael G, Cutler GB Jr, Loriaux DL, Meggs WJ, Kaliner M. Recurrent anaphylaxis in menstruating women: treatment with a luteinizing hormone-releasing hormone agonist—a preliminary report. *Obstet Gynecol*. 1987;70:542–546.
65. Stranahan D, Rausch D, Deng A, Gaspari A. The role of intradermal skin testing and patch testing in the diagnosis of autoimmune progesterone dermatitis. *Dermatitis*. 2006;17:39–42.
66. Shelley WB, Preucel RW, Spooner SS. Autoimmune progesterone dermatitis: cure by oophorectomy. *JAMA*. 1964;190:35–38.
67. Halevy S, Cohen AD, Lunenfeld E, Grossman N. Autoimmune progesterone dermatitis manifested as erythema annulare centrifugum: confirmation of progesterone sensitivity by in vitro interferon-gamma release. *J Am Acad Dermatol*. 2002;47:311–313.
68. Meggs WJ, Pescovitz OH, Metcalfe D, Loriaux DL, Cutler G Jr, Kaliner M. Progesterone sensitivity as a cause of recurrent anaphylaxis. *N Engl J Med*. 1984;311:1236–1238.
69. Sloane D, Govindarajulu U, Harrow-Mortelliti J, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. *J Allergy Clin Immunol Pract*. 2016;4:497–504.
70. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol*. 2009;124:1259–1266.
71. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122:574–580.
72. Ortmann O, Weiss JM, Diedrich K. Gonadotrophin-releasing hormone (GnRH) and GnRH agonists: mechanisms of action. *Reprod Biomed Online*. 2002;5(suppl 1):1–7.
73. Cocuroccia B, Gisondi P, Gubellini E, Girolomoni G. Autoimmune progesterone dermatitis. *Gynecol Endocrinol*. 2006;22:54–56.
74. Rodenas JM, Herranz MT, Tercedor J. Autoimmune progesterone dermatitis: treatment with oophorectomy. *Br J Dermatol*. 1998;139:508–511.