

Progestogen Hypersensitivity: Heterogeneous Manifestations with a Common Trigger



Kathleen M. Buchheit, MD^{a,b}, and Jonathan A. Bernstein, MD^c *Boston, Mass; and Cincinnati, Ohio*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: May 1, 2017. Credit may be obtained for these courses until April 30, 2018.

Copyright Statement: Copyright © 2017-2019. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical

Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.0 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Kathleen M. Buchheit, MD, and Jonathan A. Bernstein, MD

Learning objectives:

1. To define progestogen hypersensitivity and appreciate its various clinical manifestations.
2. To understand the proposed immunopathogenesis of progestogen hypersensitivity.
3. To determine the best approach to evaluate and treat patients with progestogen hypersensitivity.

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

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The authors declare that they have no relevant conflicts of interest.

Hypersensitivity to progestogen, previously known as autoimmune progesterone dermatitis, is an increasingly recognized clinical entity that presents specific diagnostic and treatment challenges. Clinical presentations are heterogeneous, but can consist of hypersensitivity symptoms associated with the progesterone surge during the luteal phase of the menstrual cycle or after exposure to exogenous progestins. With the increasing use of exogenous progesterone for contraception and fertility, more cases of hypersensitivity to exogenous progestins have been described. Here we will review proposed pathomechanisms for progestogen hypersensitivity (PH) as well as the clinical

presentation of PH, testing strategies to aid in diagnosis, and treatment options for patients with hypersensitivity to progestogens. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:566-74)

Key words: Progesterone; Progestin; Progestogen; Autoimmune progesterone dermatitis; Catamenial anaphylaxis; Desensitization; Drug allergy; Lactation anaphylaxis; Estrogen hypersensitivity; Estrogen dermatitis

The prevalence of autoimmune progesterone dermatitis (APD) is unknown but believed to be a rare condition. APD has varied manifestations ranging from immediate-type symptoms such as urticaria, asthma, or anaphylaxis to delayed-type hypersensitivity symptoms presenting as chronic dermatitis. The term APD was first coined by Shelley et al in 1964¹ and is often used to describe all progesterone hypersensitivity syndromes. However, the term APD does not accurately represent the heterogeneous clinical manifestations of hypersensitivity to progesterone and there is little evidence to support an autoimmune pathomechanism for this disease. Therefore, more recently the term progestogen hypersensitivity (PH) was proposed as a more accurate term to describe this syndrome.² Here we will review the clinical presentation, diagnosis, treatment, and possible mechanistic basis of PH and other hormonal hypersensitivity syndromes, as the allergist/immunologist is uniquely positioned to

^aDivision of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, Mass

^bDepartment of Medicine, Harvard Medical School, Boston, Mass

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

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 31, 2016; revised manuscript received and accepted for publication January 3, 2017.

Corresponding author: Jonathan A. Bernstein, MD, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML#563, Cincinnati, OH 45267-0563. E-mail: Jonathan.Bernstein@uc.edu.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.01.019>

Abbreviations used

APD- Autoimmune progesterone dermatitis
ELISA- Enzyme-linked immunosorbent assay
GnRH- Gonadotropin-releasing hormone
HRT- Hormone replacement therapy
IVF- In vitro fertilization
LHR- Leukocyte histamine release
MC- Mast cell
NSAID- Nonsteroidal anti-inflammatory drug
OCP- Oral contraceptive pill
PG- Prostaglandin
PH- Progesterone hypersensitivity
UC- Ulcerative colitis

diagnose PH and tailor treatment based on each patient's symptoms and treatment preference.

PROGESTERONE METABOLISM AND PHYSIOLOGIC ROLES

Before discussing PH, it is important to appreciate the function of progesterone. Progesterone is derived from cholesterol and its major metabolite is pregnanediol that is synthesized in the liver. Synthetic progestins are made by adding or modifying side chains. Most synthetic progestins are derived from 19-nortestosterone, 17 α -hydroxyprogesterone, or acetoxyprogesterin.³ Progesterone has a broad range of metabolic and physiologic effects related to embryogenesis, the menstrual cycle, lactation, and pregnancy.⁴ It is a member of the steroid hormone group called progestogens and is the major progestogen in the body. Progesterone is an important metabolic intermediate in the production of other endogenous steroids such as sex hormones and corticosteroids as well as a neurosteroid important in brain function.⁴ Progesterone is important for causing changes to the endometrium during the luteal phase to prepare the uterus for implantation. If pregnancy does not occur, progesterone levels decrease resulting in menstruation. During implantation and gestation, progesterone decreases the maternal immune response allowing for pregnancy.⁴ Increased progesterone levels have many other physiologic effects including decreasing uterine smooth muscle contractility and inhibition of lactation during pregnancy, and a fall in progesterone levels is believed to trigger lactation and labor. In addition, progesterone acts as an anti-inflammatory and, therefore, can regulate T-lymphocyte-mediated immune responses.⁴ Given the many roles of progesterone on a spectrum of organ systems, development of an immediate or delayed hypersensitivity response to this hormone has broad ranging implications beyond reproduction.

MAST CELL EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS

Several investigators have demonstrated the presence of estradiol (ER α and ER β) and progesterone (PRA and PRB) receptors on human, mouse, and rat mast cells (MCs).⁵ In humans, mRNA expression of ER α but not ER β has been demonstrated on MCs.^{5,6} Furthermore, it has been shown that 17 β -estradiol resulted in rapid MC activation that was inhibited by the ER antagonist, tamoxifen. Of importance, bone marrow-

derived MCs isolated from an ER α knockout mouse did not degranulate in response to 17 β -estradiol treatment indicating that the 17 β -estradiol effect on MCs is mediated through the ER α receptor.^{5,6} In addition, treatment of human MC lines *in vitro* with physiological concentrations of estradiol and progesterone resulted in significantly increased release of the MC serine proteinase marker, β -tryptase.⁵ Further investigation into the roles of PR and ER on MC in the pathomechanisms of PH discussed below is required.

POTENTIAL PATHOMECHANISMS FOR PH

The menstrual cycle (Figure 1) is controlled by complex hormonal interactions between the hypothalamus, pituitary, and ovaries. It begins with shedding of the uterine lining, then development of a mature oocyte during the follicular phase of the menstrual cycle, which correlates with rising estrogen levels.⁷ The luteal phase of the menstrual cycle starts with a luteal hormone surge, which is followed by follicular rupture, oocyte release, and then secretion of progesterone by the corpus luteum. Progesterone levels begin to rise 24 to 48 hours before ovulation and tend to peak at day 20-21 of a 28-day cycle,^{3,8,9} which prepares the uterus for implantation of the ovum. The majority of patients with hypersensitivity to endogenous progesterone experience symptoms during the peak progesterone levels of the luteal phase^{2,10} occurring the week before menstruation and dissipate a few days into menses; however, reactions can persist throughout the menstrual cycle. PH needs to be differentiated from catamenial anaphylaxis (see below), which begins during menses and can persist throughout the follicular phase.

It is unclear how patients become sensitized to progestogens. One theory is that sensitization occurs with exposure of exogenous progesterone or synthetic progestins used for contraception or hormonal supplementation, which results in formation of progestogen-specific IgE antibodies. When subsequent exposure to a progestogen occurs, patients react because of cross-linking of these antibodies.¹¹ Many cases of PH are related to supratherapeutic doses of progesterone used for fertility treatments, which further supports exogenous progestogen exposure leading to consequent hypersensitivity.^{2,12,13} However, there are multiple reports of patients who have never been exposed to exogenous progestogen who develop PH.¹⁴⁻¹⁷ An alternative proposed mechanism for sensitization is corticosteroid cross-sensitization by corticosteroids that have a similar structure to progesterone. Schoenmakers et al found that of 19 patients with hydrocortisone allergy, 5 patients had positive patch testing to 17- α -progesterone. However, only 2 patients in this study had symptoms consistent with PH.¹⁸ Furthermore, corticosteroid cross-sensitization does not explain PH in patients without documented corticosteroid allergy, and many patients with PH tolerate topical and oral corticosteroids as treatment for PH.

As discussed above, the underlying pathobiology of PH is poorly understood, but given the heterogeneity of clinical manifestations, multiple mechanisms are likely. Evidence that type I, immediate hypersensitivity plays a role in the underlying pathogenesis of PH is supported by positive immediate skin prick or intracutaneous testing to progesterone in many patients with suspected PH.^{19,20} Evidence of basophil and MC activation using functional assays also supports an IgE-mediated immune response.^{1,21,22} In patients with immediate-type symptoms suggestive of PH but with negative skin prick testing to

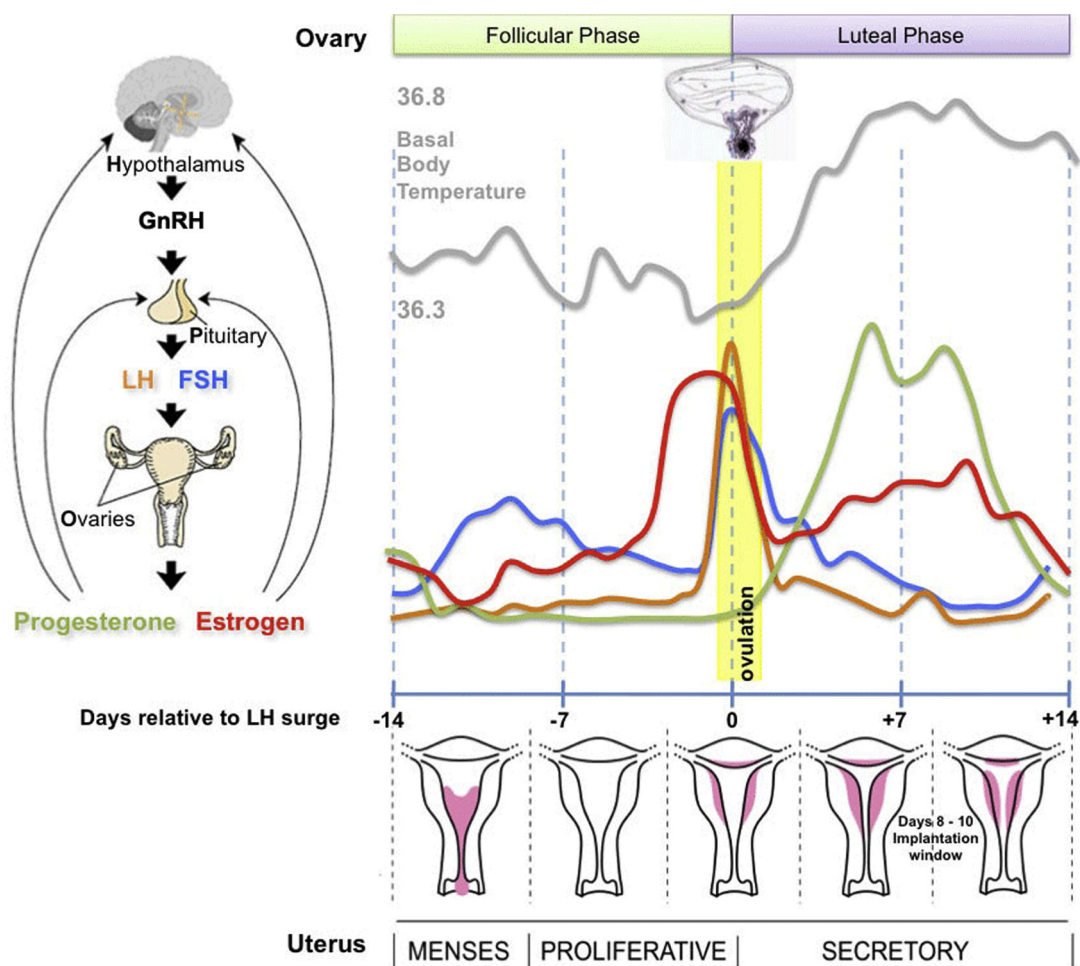


FIGURE 1. The menstrual cycle. *FSH*, Follicle stimulating hormone; *GnRH*, gonadotropin-releasing hormone; *LH*, leutinizing hormone.

progesterone, it has been proposed that progesterone can modulate MC and/or basophil reactivity causing direct hormone-induced MC activation and release of bioactive mediators. However, Slater et al studied the effect of estrogen and progesterone on histamine release by basophils and found that neither progesterone nor estrogen influenced basophil histamine release. The authors concluded that the MC was more likely to be involved in anaphylaxis related to progesterone, but given the challenge of purifying tissue-resident MCs, they could not study the effects of hormones on MCs *in vitro*.²³ The reports of delayed reactions to skin prick or intracutaneous testing may represent a late phase skin test response or support a delayed, cell-mediated mechanism.²⁴⁻²⁶

Immune complex formation and tissue deposition has also been implicated mechanistically in PH. Cheesman et al describe a patient with cyclical oral and perineal rashes who had circulating immunoglobulin directed against 17-hydroxyprogesterone with an IgG fraction containing a progesterone binding component. They proposed that antigen-antibody interactions occurring while progesterone levels rose were responsible for the patient's symptoms. Treatment with corticosteroids for 2 months reduced the IgG concentration to normal levels.²⁷ In another report, a patient with recurrent erythema

multiforme during the luteal phase of the menstrual cycle had detectable immune complexes after challenge with medroxyprogesterone.²⁸

Shelley et al¹ initially used the term *autoimmune* to describe PH because their patient reacted to endogenous progesterone; however, as discussed below, there is now ample evidence that this condition can occur with endogenous and exogenous progestogens and is more likely an immediate-type hypersensitivity reaction rather than an autoimmune response. In fact, there is scant evidence supporting PH as an autoimmune condition. In one case report, a patient was reported to have cyclical dermatitis due to PH that preceded the development of ulcerative colitis (UC) with positive perinuclear antineutrophil cytoplasmic antibodies by 2 years,²⁹ but there is no clear proof that the PH and UC were related.

EPIDEMIOLOGY

PH is a rare and poorly recognized disorder with unknown prevalence and incidence. It presents in women of childbearing age with symptoms first occurring anytime from menarche to menopause. Although PH typically affects only women, there is one case of hypersensitivity to megestrol acetate in a male,

confirmed by positive skin testing to progesterone acetate.³⁰ Both a recent literature review of 89 patients and a large case series of 24 patients found the average age of onset to be in the third decade of life, with a mean age of 27.3 years (range, 12–47 years) and 29.7 years (range, 13–48 years), respectively.^{2,10} Family history of PH is not thought to be a risk factor, but there is one case report of 3 sisters with PH.²⁶ Although risk factors for PH have not been rigorously evaluated, there does seem to be a relationship between exogenous progesterone exposure and development of the disease.^{2,10,13,31} Nguyen and Razzaque Ahmed¹⁰ found that 40 of the 89 (44.94%) cases they reviewed had known prior exposure to exogenous progesterone. Current or previous exogenous progesterone exposure is not always present and many patients experience symptoms only with endogenous progesterone exposure during menstruation or pregnancy.^{15,32}

CLINICAL CHARACTERISTICS

Symptoms of PH vary widely and include dermatologic and nondermatologic manifestations (Table I). Dermatologic findings include eczematous dermatitis,^{22,31} maculopapular rash, papules and plaques, vesiculobullous and vesiculopustular lesions,^{1,3,33} urticaria with or without angioedema,^{12,13,16,17,34,35} petechiae and purpura,^{32,36} fixed drug eruption,^{37,38} vulvovaginal pruritus,³⁹ stomatitis,^{40,41} and erythema multiforme^{28,42} (Figure 2). Nondermatologic allergic manifestations such as asthma and anaphylaxis^{17,37,43–45} can also occur. In some patients, multiple dermatologic and nondermatologic manifestations have been described.^{37,42,45,46}

The timing of symptoms is most frequently associated with the progesterone surge of the luteal phase of the menstrual cycle, typically 3 to 10 days before menses. Therefore, the cyclical nature of PH is a diagnostic clue for clinicians. However, symptoms triggered by exposure to exogenous progestins, such as those used for contraception or fertility treatments, do not necessarily correlate with the menstrual cycle and some women with PH have irregular menses. Both of these scenarios can obfuscate or delay the diagnosis of PH if the clinician is not aware of the polymorphic presentation of this condition.^{3,16} Patients with irregular menses may have endogenous progesterone hypersensitivity,¹⁶ but may also be at increased risk of PH due to exogenous progesterone exposure used to regulate the menstrual cycle. Furthermore, some patients experience symptoms of PH at other times of the menstrual cycle. The natural history of PH is also not well defined, but there are reports of patients who have been followed long-term without remission of symptoms,⁴⁵ whereas others go into remission at menopause.²⁰ There are no published reports of PH in postmenopausal women receiving progestins with hormone replacement therapy (HRT). However, epidemiological studies show an association with new asthma diagnoses after postmenopausal hormone treatment with estrogen with or without progestin.⁴⁷ PH should be considered in postmenopausal women on HRT with compatible clinical symptoms.

PH can be triggered by endogenous progesterone, which is secreted by the ovarian corpus luteum during the luteal phase of the menstrual cycle^{16,48} or by the corpus luteum and/or placenta during pregnancy.^{24,49} Among patients with pregnancy-associated symptoms, PH can begin intrapartum, and may or may not continue after childbirth.^{25,50,51} PH can also start in the postpartum period, suggesting sensitization to high levels of

TABLE I. Clinical findings*

Dermatologic	Eczematous dermatitis
	Urticaria
	Angioedema
	Pruritus
	Stomatitis
	Erythema multiforme
	Petechiae/purpura
Nondermatologic	Fixed drug eruption
	Vesiculobullous/vesiculopustular lesions
	Asthma
	Anaphylaxis

*Multiple simultaneous clinical manifestations occur in many patients.

progesterone present during pregnancy.^{1,33,52} There are reports of patients with PH, who developed worsening of symptoms during pregnancy as systemic progesterone levels rose,^{28,51} and paradoxically patients with PH before pregnancy who improved in the intrapartum period.^{17,53} It has been proposed that intrapartum improvement may be due to either autodesensitization to progesterone as it rises gradually during pregnancy, or an attenuation of maternal immune responses during pregnancy.³³

PH can also be triggered by progestins in oral contraceptive pills (OCPs),^{3,31,45} long-acting depot progestin preparations such as medroxyprogesterone acetate,^{16,43,53} progestin-containing vaginal rings,⁵⁴ and progestin-containing intrauterine devices.² Notably, high-dose progesterone required for *in vitro* fertilization (IVF) can induce PH, which can limit the patient's ability to tolerate fertility treatment and achieve a desired pregnancy.³¹ A recent classification system based on endogenous versus exogenous triggers of PH has been proposed to facilitate diagnosis and classification across specialties and focus attention on exposures in addition to symptoms (Table II).²

DIAGNOSIS

The diagnosis of PH is primarily based on a clinical history of hypersensitivity symptoms correlating with the luteal phase of the menstrual cycle, or symptoms correlating with exposure to exogenous progesterogens. A careful clinical history is required to evaluate other potential triggers, such as nonsteroidal anti-inflammatory drugs (NSAIDs) that are commonly used in the premenstrual period,⁵⁴ and exclusion of other diseases such as chronic idiopathic urticaria, atopic dermatitis, and allergic contact dermatitis. However, when a high level of clinical suspicion for PH exists, other testing modalities, such as progesterone skin testing, progesterone challenge, and several *in vitro* assays, are used to confirm the diagnosis.

Progesterone skin prick and intracutaneous testing has been employed as a diagnostic test to confirm suspected PH.^{12,35,55} This test has been proposed to be helpful for identifying both immediate^{2,20} and delayed^{25,26,56} hypersensitivity in PH. Autologous serum skin tests, with sera obtained during the follicular and luteal phases of the menstrual cycle, have also been proposed as a useful tool for diagnosis of PH.⁵⁵ The skin prick test with full concentration pharmaceutical grade progesterone (50 mg/mL) has been recommended followed by intracutaneous tests with dilutions starting at a 1:1000 w/v concentration and

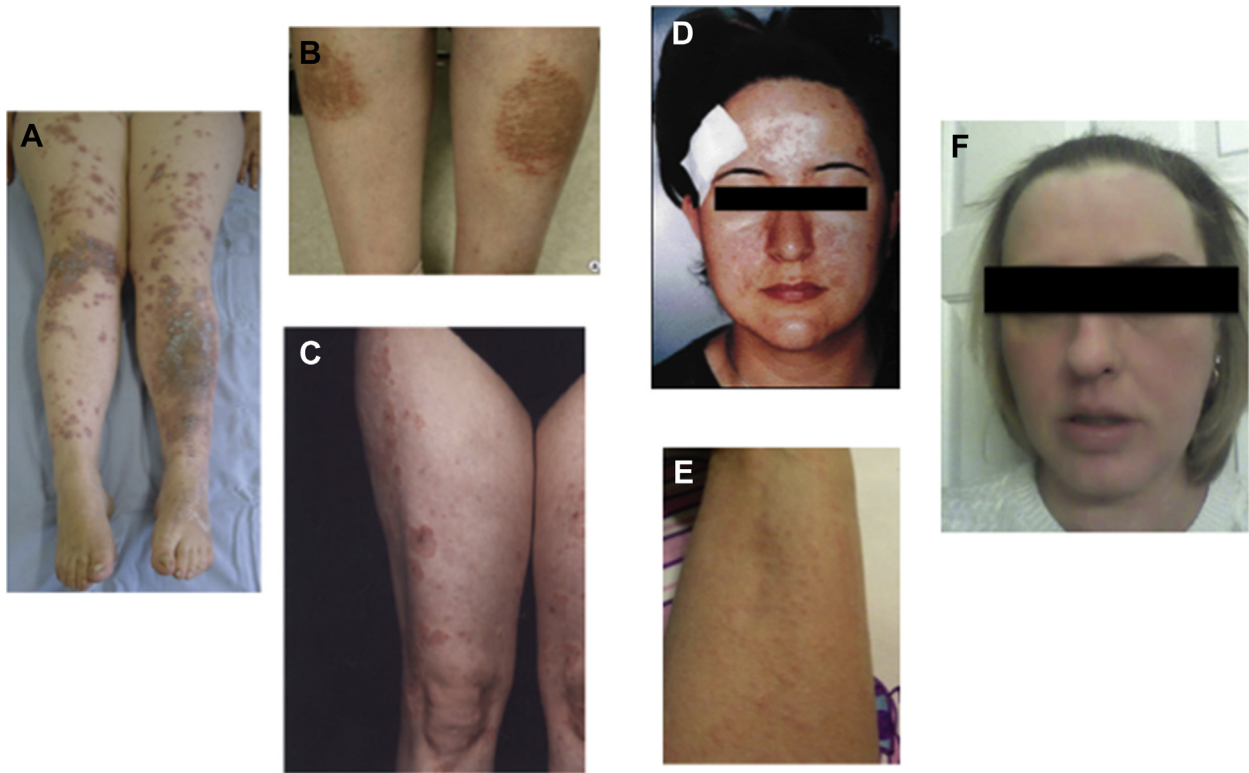


FIGURE 2. The polymorphic cutaneous manifestations of progesterone hypersensitivity. **A**, Pustules and plaques; **B**, nummular eczematous dermatitis; **C**, annular targetoid plaques; **D**, maculopapular rash; **E**, eczematous dermatitis; and **F**, angioedema/urticaria.

TABLE II. Classification of progesterone hypersensitivity (aka autoimmune progesterone dermatitis)

Classification	Triggers	Manifestation
Endogenous		
Primary	Menses	Perimenstrual symptoms
	Pregnancy	Monthly symptoms after completion of non-IVF pregnancy
Exogenous		
Secondary	Supplemental progesterone*	Symptoms only during supplemental progesterone administration
Mixed†	Supplemental progesterone*	Took supplemental progesterone, then develops perimenstrual symptoms

IVF, *In vitro* fertilization.

From Foer et al.²

*Includes nonnative progesterone and progestins.

†Defined as an initial reaction due to exogenous exposure, with subsequent reactions to both exogenous and endogenous sources of progesterone.

increasing to a 1:10 w/v concentration in conjunction with appropriate negative saline and positive histamine controls.^{2,12} As progesterone is not water soluble, it has to be suspended in an ethanol or oil diluent. This can frequently lead to a false-positive reaction given the irritating nature of the ethanol or oil diluent, which thus limits the positive predictive utility of skin testing as a diagnostic tool.^{2,56} Given the irritant reactions, the ethanol or oil diluent without progesterone should be used as a control. Intracutaneous testing with synthetic progestins has been described^{55,57}; however, synthetic progestins often contain

additives such as polyethylene glycol. Thus, although skin prick and intracutaneous testing are used frequently to confirm suspected cases of PH, the positive and negative predictive value of skin testing is unknown and preparations of skin test reagents are not standardized. Furthermore, although positive skin testing can confirm a diagnosis in a patient with a compatible clinical history, negative skin testing does not rule out PH. Progesterone patch testing has been attempted, but has not been shown to be a useful diagnostic modality.⁵⁸

Progesterone challenge has been used in the diagnosis of PH.^{1,28} Although provocation can be useful to confirm suspected PH in patients with an unclear diagnosis, it can aggravate the patient's severe dermatitis thereby leading to significant prolonged morbidity. Therefore, progesterone challenge should be used judiciously given the associated risks. When possible, alternative strategies should be employed such as skin testing, empiric treatment tailored to specific symptoms, or empiric progesterone desensitization.

A number of experimental *in vitro* tests have been used to diagnose or confirm PH. Bernstein et al describe a direct leukocyte histamine release (LHR) assay on basophils from a patient with recurrent anaphylaxis, cyclic urticaria and angioedema, and dermatitis. The LHR assay remained persistently positive to 5-pregnandiol, and was inhibited by an antiprogesterone mouse monoclonal antibody and mifepristone, a progesterone inhibitor. The patient was also found to have progesterone-specific IgE by enzyme-linked immunosorbent assay (ELISA).⁴⁵ Interferon- γ -release assay, as a way to assess drug-related T-cell activity,⁵² has also been proposed. However, the most practical

TABLE III. Treatment options in progesterone 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.

and reliable assay for identifying an IgE-mediated immune response is by ELISA. Regardless of whether an *in vitro* assay or skin testing is used to confirm immediate hypersensitivity, a functional histamine release assay would be ideal for confirming the predictive value of quantitative/semiquantitative specific IgE antibody assays like ELISA. The availability of this functional assay could obviate the need for progesterone provocation in the future.

TREATMENT

Treatment for PH varies widely based on symptoms and long-term goals, but generally focuses on controlling specific symptoms or inducing anovulation if appropriate. The various treatments that have been reported for PH are summarized in Table III. Antihistamines have been trialed for relief of pruritus, urticaria, and angioedema with variable rates of success. Some patients have reported experiencing relief,^{17,44,46} whereas others have not had improvement.⁵⁹ Topical and oral glucocorticoids have both shown to have efficacy in some studies,^{27,31} but are not a viable long-term option for many patients due to the potential for adverse systemic side effects.

OCPs have been used to suppress ovulation, but because they contain both estrogen and progestins, these agents are frequently not well tolerated.⁵³ In this circumstance, desensitization to OCPs has been successful.²

Gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate, have been used to treat PH in patients with severe symptoms refractory to other medical therapies.^{16,44,45,53,60,61} At doses used to suppress ovulation, these agents work by inhibiting pituitary gonadotropin release, thus resulting in inhibition of ovulation and suppression of luteal progesterone.⁶² Slater et al conducted a small, double-blind crossover study of a GnRH agonist in 4 women with a history of recurrent idiopathic anaphylaxis. Only 2 of the 4 patients improved on the GnRH agonist, and the 2 who improved demonstrated positive skin testing to medroxyprogesterone acetate and anaphylaxis to luteinizing hormone-releasing hormone infusion, indicating that the GnRH responders had PH.⁶¹ Although GnRH agonists can successfully treat PH, they must be used with caution in PH given their unfavorable side-effect profile. Most side effects from GnRH agonists result from the suppression of estrogen, and include amenorrhea, hot flashes, urogenital atrophy, and bone

loss.⁶³ Women requiring treatment with GnRH agonists over 6 to 12 months are at increased risk for osteopenia and osteoporosis,^{64,65} which limits the use of these agents in PH because it requires long-term inhibition of ovulation for amelioration of symptoms. Furthermore, GnRH agonists are not a feasible long-term option in younger women with PH who desire to conceive.

Symptoms consistent with immediate and delayed hypersensitivity have been successfully treated with progesterone desensitization.^{2,13,17} The exact mechanism by which desensitization to progesterone induces tolerance is unknown, but may be secondary to IgE-dependent tolerance observed with desensitization to other drugs.⁶⁶⁻⁶⁸ Indications for desensitization include severe symptoms not controlled with standard medications such as progestin containing OCPs or antihistamines.² Another indication for desensitization is the need for high-dose progesterone for medical treatment, as is required for IVF.^{13,17} Rapid progesterone desensitization has been used to relieve urticaria and angioedema triggered by progesterone exposure.¹⁷ This treatment has also been utilized in patients who need carefully timed tolerance of progesterone to coincide with fertility treatment, such as before embryo transfer in IVF.^{2,13} Successful rapid desensitization protocols have been described to oral, intravaginal, and intramuscular progesterone.^{2,12,13} Pretreatment should be tailored to the patient's specific symptoms. Successful pretreatment regimens include antihistamines and oral corticosteroids.¹⁷ Slow oral desensitization protocols have also been used successfully in patients with dermatitis-type symptoms. One such protocol is to use a combined OCP containing estrogen and progestin. After desensitization patients are continuously cycled on the OCP, so that there is no cessation of progesterone exposure leading to resensitization.² Figure 3 provides examples of slow and rapid oral desensitization protocols as well as an intramuscular protocol that have been successfully used for treatment of PH.^{2,13}

Stanozolol and danazol, 17- α -alkylated steroids, have been used successfully in combination with glucocorticoids for premenstrual flares of chronic urticaria;^{50,59} however, undesirable side effects of hirsutism, mood changes, and increased liver function tests limit their use. Tamoxifen, a selective estrogen-receptor modulator, has also been used to suppress ovulation in patients with PH,^{28,41,48} but by blocking endogenous estrogen, tamoxifen can cause symptoms of hypoestrogenemia similar to GnRH agonists discussed above.

A	Day	Dose (based on progestin 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		

FIGURE 3. Oral and intramuscular progestin desensitization protocols. **A**, Slow oral protocol. **B**, Two-day oral protocol. **C**, Rapid IM protocol. *IM*, Intramuscular; *IVF*, *in vitro* fertilization. Reproduced with permission from Foer et al.² and Prieto-Garcia et al.¹³

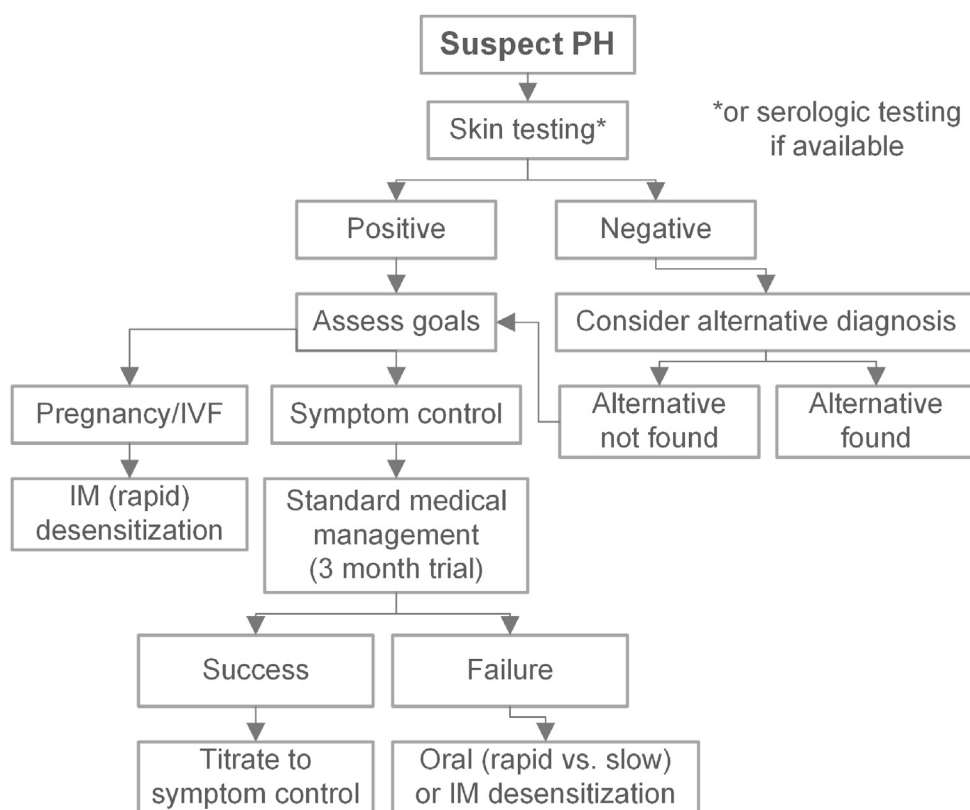


FIGURE 4. Algorithmic approach for evaluation and treatment of progesterogen hypersensitivity. *IM*, Intramuscular; *IVF*, *in vitro* fertilization; *PH*, progesterogen hypersensitivity. Reproduced with permission from Foer et al.²

Oophorectomy has been employed as a definitive treatment for patients with severe PH that cannot otherwise be managed medically.^{1,14,15,40} Certainly this approach would be a last resort for the most severe refractory cases and preferably not in women who still wish to conceive.

The allergist/immunologist is positioned to work closely with dermatologists, gynecologists, and reproductive endocrinologists to optimize treatment of PH and meet individual patient goals. Figure 4 provides an algorithmic approach to the evaluation and treatment of a patient with suspected PH.²

OTHER REPRODUCTIVE HORMONE HYPERSENSITIVITY SYNDROMES

Estrogen hypersensitivity

Hypersensitivity to endogenous and exogenous estrogens has also been described in several case series and case reports.⁶⁹⁻⁷³ This syndrome has been called estrogen dermatitis, and characteristically presents as a premenstrual flare of urticaria or a delayed-type dermatitis.⁶⁹ It is confirmed by a positive immediate or delayed intracutaneous estrogen test^{69,70} or an estrogen challenge.⁷¹ Estrogen suppression with tamoxifen,^{69,70} leuprolide acetate,⁷⁴ progestin-only contraceptive,⁷³ and oophorectomy⁷¹ has been used successfully to treat this condition. In patients with symptoms related to exogenous estrogen exposure, withdrawal of oral estrogen therapy is advised and has been effective.⁶⁹ Although the etiology of the syndrome remains unknown, a dendritic cell-mediated allergic mechanism has been postulated.⁷²

Catamenial anaphylaxis

Catamenial anaphylaxis and dermatoses are also temporally associated with the menstrual cycle, but the timing differs from symptoms associated with PH. In catamenial anaphylaxis, symptoms correlate with the onset of the menstrual cycle, not the period of peak progesterone concentrations before the onset of menses as observed with PH.⁴³ Catamenial anaphylaxis occurs when progesterone and estrogen levels decline significantly at the onset of menses (Figure 1). However, some also use the term catamenial anaphylaxis to describe premenstrual reactions to progesterone.^{57,75} It has been proposed that catamenial symptoms coinciding with the onset of menses are triggered by endometrial release of prostaglandins (PGs), which are highest on day 1 of the menstrual cycle.^{76,77} PGF₂ is synthesized by the endometrium⁷⁸ and is related to mediator release by uterine MCs.⁷⁹ Differentiating between PH and catamenial symptoms may be important, as different treatments for catamenial symptoms have been proposed. Burstein et al report a patient with recurrent anaphylaxis occurring in the first 24 hours after onset of menses, who had improvement of symptoms after treatment with indomethacin, which inhibits PGs. Complete resolution of the patient's symptoms occurred after hysterectomy and salpingo-oophorectomy.⁷⁶

Lactation-associated anaphylaxis

Anaphylaxis associated with lactation is very rare, and there are few reported cases.⁸⁰⁻⁸⁵ In most cases, the onset of symptoms occurs in the first few days after delivery and is associated with the act of breastfeeding or manual expression of breast milk. The anaphylactic events have been associated with elevated serum tryptase.⁸¹ Symptoms can occur with subsequent pregnancies.^{82,83} The underlying cause of lactation-associated anaphylaxis is not well understood, but it has been proposed that the rapid decrease in progesterone leads to an exaggerated histamine response.⁸⁵ The theory of hypersensitivity to hormones associated with lactation such as prolactin and oxytocin has also been explored, but no positive skin testing to these hormones has been elicited in patients with lactation-associated anaphylaxis.^{82,85}

It is also possible that the use of NSAIDs in the postpartum period may be responsible for the anaphylactic event,^{80,82,85} as NSAIDs are commonly used for postpartum pain control. In some patients, the symptoms resolve after several days of breastfeeding.⁸² When symptoms do not resolve, treatment with suppression of lactation^{83,85} is optimal.

CONCLUSIONS

A number of syndromes associated with hypersensitivity to female reproductive hormones exist. Hypersensitivity to progesterone is most commonly reported, but there are also hypersensitivity syndromes associated with estrogen exposure, menstruation, and lactation. Prompt recognition of these syndromes will allow for appropriate treatment of the hypersensitivity symptoms, which involves collaboration with the patient's primary care doctor and/or gynecologist to employ the most appropriate treatment intervention(s) taking into account efficacy, safety, and patient preference.

REFERENCES

1. Shelley WB, Preucel RW, Spont SS. Autoimmune progesterone dermatitis. Cure by oophorectomy. *JAMA* 1964;190:35-8.
2. 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;4:723-9.
3. Hart R. Autoimmune progesterone dermatitis. *Arch Dermatol* 1977;113:426-30.
4. Taraborrelli S. Physiology, production and action of progesterone. *Acta Obstet Gynecol Scand* 2015;94(Suppl 161):8-16.
5. Zierau O, Zenclussen AC, Jensen F. Role of female sex hormones, estradiol and progesterone, in mast cell behavior. *Front Immunol* 2012;3:169.
6. Zaitu M, Narita S, Lambert KC, Grady JJ, Estes DM, Curran EM, et al. Estradiol activates mast cells via a non-genomic estrogen receptor- α and calcium influx. *Mol Immunol* 2007;44:1977-85.
7. Owen JA Jr. Physiology of the menstrual cycle. *Am J Clin Nutr* 1975;28:333-8.
8. Forbes TR. Systemic plasma progesterone levels during the human menstrual cycle. *Am J Obstet Gynecol* 1950;60:180-6.
9. Stocco C, Telleria C, Gibori G. The molecular control of corpus luteum formation, function, and regression. *Endocr Rev* 2007;28:117-49.
10. Nguyen T, Razzaque Ahmed A. Autoimmune progesterone dermatitis: update and insights. *Autoimmun Rev* 2016;15:191-7.
11. Meltzer L. Hypersensitivity to gonadal hormones. *South Med J* 1963;56:538-42.
12. Hill JL, Carr TF. Iatrogenic autoimmune progesterone dermatitis treated with a novel intramuscular progesterone desensitization protocol. *J Allergy Clin Immunol Pract* 2013;1:537-8.
13. 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-e13.
14. Rodenas JM, Herranz MT, Tercedor J. Autoimmune progesterone dermatitis: treatment with oophorectomy. *Br J Dermatol* 1998;139:508-11.
15. Moody BR, Schatten S. Autoimmune progesterone dermatitis: onset in a woman without previous exogenous progesterone exposure. *South Med J* 1997;90:845-6.
16. 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.
17. Poole JA, Rosenwasser LJ. Chronic idiopathic urticaria exacerbated with progesterone therapy treated with novel desensitization protocol. *J Allergy Clin Immunol* 2004;114:456-7.
18. Schoenmakers A, Vermorken A, Degreef H, Doooms-Gossens A. Corticosteroid or steroid allergy? *Contact Derm* 1992;26:159-62.
19. Kaygusuz I, Gumus II, Sarifakioglu E, Eser A, Bozkurt B, Kafali H. Autoimmune progesterone dermatitis. *Taiwan J Obstet Gynecol* 2014;53:420-2.
20. Lee MK, Lee WY, Yong SJ, Shin KC, Lee SN, Lee SJ, et al. A case of autoimmune progesterone dermatitis misdiagnosed as allergic contact dermatitis. *Allergy Asthma Immunol Res* 2011;3:141-4.
21. Miura T, Matsuda M, Yanbe H, Sugiyama S. Two cases of autoimmune progesterone dermatitis. Immunohistochemical and serological studies. *Acta Derm Venereol* 1989;69:308-10.
22. Jones WN, Gordon VH. Auto-immune progesterone eczema. An endogenous progesterone hypersensitivity. *Arch Dermatol* 1969;99:57-9.
23. Slater JE, Kaliner M. Effects of sex hormones on basophil histamine release in recurrent idiopathic anaphylaxis. *J Allergy Clin Immunol* 1987;80(Pt 1):285-90.
24. Georgouras K. Autoimmune progesterone dermatitis. *Australas J Dermatol* 1981;22:109-12.
25. Teelucksingh S, Edwards CR. Autoimmune progesterone dermatitis. *J Intern Med* 1990;227:143-4.
26. Chawla SV, Quirk C, Sondheimer SJ, James WD. Autoimmune progesterone dermatitis. *Arch Dermatol* 2009;145:341-2.

27. 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;55:597-9.
28. Wojnarowska F, Greaves MW, Peachey RD, Drury PL, Besser GM. Progesterone-induced erythema multiforme. *J R Soc Med* 1985;78:407-8.
29. Naito T, Matsuyama S, Ogawa K, Sekigawa I, Iida N, Shimizu K, et al. Ulcerative colitis associated with autoimmune progesterone dermatitis. *J Clin Gastroenterol* 1997;25:488-9.
30. Fisher DA. Drug-induced progesterone dermatitis. *J Am Acad Dermatol* 1996;34(Pt 1):863-4.
31. Jenkins J, Geng A, Robinson-Bostom L. Autoimmune progesterone dermatitis associated with infertility treatment. *J Am Acad Dermatol* 2008;58:353-5.
32. Wintzen M, Goor-van Egmond MB, Noz KC. Autoimmune progesterone dermatitis presenting with purpura and petechiae. *Clin Exp Dermatol* 2004;29:316.
33. Herzberg AJ, Strohmeyer CR, Cirillo-Hyland VA. Autoimmune progesterone dermatitis. *J Am Acad Dermatol* 1995;32(Pt 2):333-8.
34. Farah FS, Shbaklu Z. Autoimmune progesterone urticaria. *J Allergy Clin Immunol* 1971;48:257-61.
35. Vasconcelos C, Xavier P, Vieira AP, Martinho M, Rodrigues J, Bodas A, et al. Autoimmune progesterone urticaria. *Gynecol Endocrinol* 2000;14:245-7.
36. 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.
37. 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;41:447-8.
38. Asai J, Katoh N, Nakano M, Wada M, Kishimoto S. Case of autoimmune progesterone dermatitis presenting as fixed drug eruption. *J Dermatol* 2009;36:643-5.
39. Banerjee AK, de Chazal R. Chronic vulvovaginal pruritus treated successfully with GnRH analogue. *Postgrad Med J* 2006;82:e22.
40. Berger H. Progesterone. *Arch Dermatol* 1969;100:117.
41. Moghadam BK, Hersini S, Barker BF. Autoimmune progesterone dermatitis and stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;85:537-41.
42. Maguire T. Autoimmune progesterone dermatitis. *Dermatol Nurs* 2009;21:190-2.
43. Snyder JL, Krishnaswamy G. Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review. *Ann Allergy Asthma Immunol* 2003;90:469-77. quiz 77, 571.
44. 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;311:1236-8.
45. Bernstein IL, Bernstein DI, Lummus ZL, Bernstein JA. A case of progesterone-induced anaphylaxis, cyclic urticaria/angioedema, and autoimmune dermatitis. *J Womens Health* 2011;20:643-8.
46. Walling HW, Scupham RK. Autoimmune progesterone dermatitis. Case report with histologic overlap of erythema multiforme and urticaria. *Int J Dermatol* 2008;47:380-2.
47. Barr RG, Wentowski CC, Grodstein F, Somers SC, Stampfer MJ, Schwartz J, et al. Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 2004;164:379-86.
48. Cocuroccia B, Gisoni P, Gubinelli E, Girolomoni G. Autoimmune progesterone dermatitis. *Gynecol Endocrinol* 2006;22:54-6.
49. Bierman SM. Autoimmune progesterone dermatitis of pregnancy. *Arch Dermatol* 1973;107:896-901.
50. Brestel EP, Thrush LB. The treatment of glucocorticosteroid-dependent chronic urticaria with stanozolol. *J Allergy Clin Immunol* 1988;82:265-9.
51. Medeiros S, Rodrigues-Alves R, Costa M, Afonso A, Rodrigues A, Cardoso J. Autoimmune progesterone dermatitis: treatment with oophorectomy. *Clin Exp Dermatol* 2010;35:e12-3.
52. 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;47:311-3.
53. Toms-Whittle LM, John LH, Griffiths DJ, Buckley DA. Autoimmune progesterone dermatitis: a diagnosis easily missed. *Clin Exp Dermatol* 2011;36:378-80.
54. Camoes S, Sampaio J, Rocha J, Tiago P, Lopes C. Autoimmune progesterone dermatitis: case report of an unexpected treatment reaction [e-pub ahead of print]. *Australas J Dermatol* 2016. <https://dx.doi.org/10.1111/ajd.12529>.
55. Garcia-Ortega P, Scorza E. Progesterone autoimmune dermatitis with positive autologous serum skin test result. *Obstet Gynecol* 2011;117(Pt 2):495-8.
56. Baer RL, Witten VH, Allen JR. Skin tests with endocrine substances; method of Zondek and Bromberg. *Ann Allergy* 1948;6:239-51.
57. Bauer CS, Kampitak T, Messieh ML, Kelly KJ, Vadas P. Heterogeneity in presentation and treatment of catamenial anaphylaxis. *Ann Allergy Asthma Immunol* 2013;111:107-11.
58. 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.
59. Shahar E, Bergman R, Pollack S. Autoimmune progesterone dermatitis: effective prophylactic treatment with danazol. *Int J Dermatol* 1997;36:708-11.
60. Yee KC, Cunliffe WJ. Progesterone-induced urticaria: response to busserelin. *Br J Dermatol* 1994;130:121-3.
61. 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;70:542-6.
62. 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.
63. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: can a consensus be reached? Add-Back Consensus Working Group. *Fertil Steril* 1999;71:420-4.
64. Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Lupron Add-Back Study Group. Obstet Gynecol* 1998;91:16-24.
65. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 2002;99(Pt 1):709-19.
66. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
67. 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;124:1259-66.
68. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. *J Allergy Clin Immunol Pract* 2016;4:497-504.
69. Shelley WB, Shelley ED, Talanin NY, Santoso-Pham J. Estrogen dermatitis. *J Am Acad Dermatol* 1995;32:25-31.
70. Leylek OA, Unlu S, Ozturkcan S, Cetin A, Sahin M, Yildiz E. Estrogen dermatitis. *Eur J Obstet Gynecol Reprod Biol* 1997;72:97-103.
71. Mayou SC, Charles-Holmes R, Kenney A, Black MM. A premenstrual urticarial eruption treated with bilateral oophorectomy and hysterectomy. *Clin Exp Dermatol* 1988;13:114-6.
72. Yotsumoto S, Shimomai K, Hashiguchi T, Uchimiya H, Usuki K, Nishi M, et al. Estrogen dermatitis: a dendritic-cell-mediated allergic condition. *Dermatology* 2003;207:265-8.
73. Randall K, Steele R. Estrogen dermatitis: treatment with progestin-only pill. *Arch Dermatol* 2005;141:792-3.
74. Yoon TY, Kim YG, Kim MK. Estrogen dermatitis responding to leuprolide acetate. *J Dermatol* 2005;32:405-6.
75. Lieberman P. Catamenial anaphylaxis. *J Allergy Clin Immunol Pract* 2014;2:358-9.
76. Burstein M, Rubinow A, Shalit M. Cyclic anaphylaxis associated with menstruation. *Ann Allergy* 1991;66:36-8.
77. Verdolini R, Atkar R, Clayton N, Hasan R, Stefanato CM. Catamenial dermatoses: has anyone ever considered prostaglandins? *Clin Exp Dermatol* 2014;39:509-12.
78. 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;121:1003-6.
79. Rudolph MI, Reinicke K, Cruz MA, Gallardo V, Gonzalez C, Bardisa L. Distribution of mast cells and the effect of their mediators on contractility in human myometrium. *Br J Obstet Gynaecol* 1993;100:1125-30.
80. McKinney KK, Scranton SE. A case report of breastfeeding anaphylaxis: successful prophylaxis with oral antihistamines. *Allergy* 2011;66:435-6.
81. Durgakeri P, Jones B. A rare case of lactation anaphylaxis. *Australas Med J* 2015;8:103-5.
82. Shank JJ, Olney SC, Lin FL, McNamara MF. Recurrent postpartum anaphylaxis with breast-feeding. *Obstet Gynecol* 2009;114(Pt 2):415-6.
83. Villalta D, Martelli P. A case of breastfeeding anaphylaxis. *Eur Ann Allergy Clin Immunol* 2007;39:26-7.
84. MacDonald JW, Ito S. Breastfeeding anaphylaxis case study. *J Hum Lact* 1998;14:243-4.
85. Mullins RJ, Russell A, McGrath GJ, Smith R, Sutherland DC. Breastfeeding anaphylaxis. *Lancet* 1991;338:1279-80.

Reproduced with permission of copyright owner.
Further reproduction prohibited without
permission.