

Progestogen Hypersensitivity in 24 Cases: Diagnosis, Management, and Proposed Renaming and Classification



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What is already known about this topic? Progestogen hypersensitivity causes heterogeneous symptoms including dermatitis, urticaria, asthma, and anaphylaxis.

What does this article add to our knowledge? It adds in-depth knowledge about progestogen hypersensitivity presentation, diagnostic testing, and management including progestogen desensitization.

How does this study impact current management guidelines? The authors propose a new naming and classification system to facilitate diagnosis and management for future study as well as a treatment algorithm for patients presenting with progestogen hypersensitivity.

BACKGROUND: Autoimmune progesterone dermatitis is a poorly recognized syndrome associated with a hypersensitivity to progestogens. Symptoms present heterogeneously, which may complicate diagnosis. Management has generally centered on symptomatic control with medication. Recently, an increasing number of cases have been reported with *in vitro* fertilization (IVF). Desensitization to progestogens is suggested as an approach to tolerate fertility treatments and provide symptom control. **OBJECTIVES:** To describe the diagnosis and management of progestogen hypersensitivity (PH) and to detail the use of

desensitization. We also propose a new terminology of progestogen hypersensitivity instead of autoimmune progesterone dermatitis, and a classification system based on exogenous and endogenous progestogen triggers to facilitate diagnosis and management.

METHODS: Twenty-four cases of PH were evaluated retrospectively. Symptom presentation, diagnostic modalities, desensitization protocols, and outcomes were analyzed.

RESULTS: Symptom onset was classified as a reaction to either endogenous progesterone (42%) or exogenous progestogens (58%). Symptoms were heterogeneous and included cyclical dermatitis, urticaria, angioedema, asthma, and anaphylaxis.

Triggers were also heterogeneous and included progesterone as well as progestins. Eleven patients underwent intramuscular (27%) or oral (73%) desensitization. Desensitization resulted in symptom control in 8 patients, IVF medication tolerance in 3 patients, and 2 pregnancies.

CONCLUSIONS: This is the largest case series of patients with PH with successful treatment outcomes. The new terminology progestogen hypersensitivity more accurately represents the diversity of presentations to endogenous or exogenous progestogens. We demonstrate that progestogen desensitization is successful in multiple patients and can result in symptom control and fertility. Women with cyclical allergic symptoms, including those undergoing IVF, should be evaluated for PH. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:723-9)

Key words: Progesterone; Progestogen; Infertility; Progestin; Desensitization; Autoimmune progesterone dermatitis; Catamenial anaphylaxis

Autoimmune progesterone dermatitis (APD) is a poorly recognized, complex syndrome occurring in women of child-bearing age. First described in the medical literature in 1964 by Shelley et al¹ as a dermatitis flare related to premenstrual

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Conflicts of interest: A. R. Gargiulo has received consultancy fees from Medcaroid and OmniGuide. M. Castells is on the boards for the American Academy of Allergy, Asthma & Immunology (AAAAI), Board of Directors, and Association of American Medical Colleges; has received consultancy fees from Merck, Sanofi, Allergy Therapeutics, and Neurophage; is employed by Brigham & Women's Hospital; has received research support from Ovarians for the Cure; and has received travel support from American College of Allergy, Asthma, and Immunology, European Competence Network on Mastocytosis, AAAAI, Federation of American Societies for Experimental Biology, and Texas Allergy, Asthma, and Immunology Society. P. G. Wickner has received consultancy fees from AMAG Pharmaceuticals; has received research support from Brigham and Women's Physician Organization Grants; and has received travel support from World Allergy Organization as a speaker. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 16, 2015; revised February 29, 2016; accepted for publication March 8, 2016.

Available online April 16, 2016.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2016.03.003>

Abbreviations used

APD- autoimmune progesterone dermatitis
 BWH- Brigham and Women's Hospital
 IM- intramuscular
 IVF- in vitro fertilization
 OCP- oral contraceptive pill
 PH- progesterone hypersensitivity

progesterone exposure, subsequent case series have reported hypersensitivity reactions to exogenous sources of progestogens² as well as endogenous progesterone^{3,4} related to menses or pregnancy.

Symptoms of APD present heterogeneously, and can range from dermatitis^{1,5,6} to dyspnea, cough, and anaphylaxis^{7,8} though patients often report multiple manifestations.^{2,3,9-14} This heterogeneity may delay diagnosis by years.⁶ Despite the identification of APD in the literature more than 40 years ago,^{1,15} the definitive underlying pathogenesis remains unknown. Broadly, symptoms may be considered a type I or type IV hypersensitivity mediated by a T_H2 rather than T_H1 response,¹⁶ which is supported by positive skin test results.^{17,18} An autoimmune explanation for APD has also been proposed.^{12,19}

The heterogeneity in presentation is paralleled by the variety of approaches to management. These include topical or systemic corticosteroids and antihistamines^{7,17} for symptomatic relief. Endogenous progesterone suppression via anovulatory therapies has been pursued with hormone antagonists^{20,21} and agonists.^{14,22} To date, bilateral oophorectomy^{1,23-25} continues to be used when alternative therapies fail to achieve symptom control.

Significantly, an increasing number of APD cases have been reported with the advent and increasing use of *in vitro* fertilization (IVF), during which women are exposed to supraphysiologic levels of progesterone.¹ In this setting, previously used approaches for symptom control and surgical interventions are no longer sufficient given the need for high-dose progesterone to support pregnancy with the ultimate goal of fertility. Desensitization represents an option for women with progestogen hypersensitivity (PH) seeking pregnancy. Intravaginal, intramuscular (IM), and oral desensitization protocols to progestogens have been described in single or small case series.^{26,27} Here, we present the largest case series of patients with PH that highlights progestogen desensitization protocols resulting in symptom resolution and successful pregnancy. We also propose a new name instead of APD, progestogen hypersensitivity, to reflect the heterogeneity of presentation as described above. We also suggest a classification for PH to facilitate diagnosis and management.

METHODS

Twenty-four cases of patients with APD followed at the Brigham and Women's Hospital (BWH) (Boston, Mass) Allergy and Immunology clinic were retrospectively reviewed. The diagnosis of APD was made on the basis of clinical history of urticaria, angioedema, dermatitis, airway obstruction, or anaphylaxis after exposure to either endogenous or exogenous progestogen (Table I). All patients underwent skin prick and intradermal skin testing to progesterone, with the concentration of progesterone for skin prick testing being 50 mg/mL and for intradermal skin testing being 0.005, 0.05, and 0.5 mg/mL with either benzyl alcohol or olive oil as a diluent. Eleven patients

TABLE I. Characteristics of patients with PH (N = 24)

	Value
Medical history	
Age of onset (y), mean (range)	29.7 (13-48)
Endogenous progesterone trigger, %	42
Exogenous progestogen trigger, %	58
	25 OCP
	25 IVF
	4 Emergency contraception
	4 IUD
Relation to menses, %	75% within week before menses
Atopy*	46%
Symptoms, %	
Dermatologic†	54 Dermatitis‡
	54 Urticaria/angioedema
Asthma	13
Anaphylaxis	8
Positive skin testing, %	50
Diagnostic modality	
	Concentration progesterone (mg/mL)§
Skin test	50
Intradermal	0.005
	0.05
	0.5

IUD, Intrauterine device.

*Defined as history of asthma, eczema, food or environmental allergies.

†Includes patients with multiple dermatologic manifestations.

‡As documented by clinicians at patient visit.

§Diluent was either benzyl alcohol or olive oil.

underwent progestogen desensitization (Tables II and III). Slow oral progestogen desensitization was initiated in the clinic and completed on outpatient basis for patients not undergoing fertility treatments. Rapid IM progesterone desensitization was completed in the BWH outpatient infusion center for patients needing precise timing of desensitization for fertility treatments or for patients with more severe reactions such as anaphylaxis.

Progesterone used for IM desensitization was prepared by the BWH pharmacy as 50 mg/mL suspended in sesame oil. Given the oil base, the doses could not be diluted with a water-soluble solution. Therefore, incremental concentrations were achieved by varying the volume only. For example, to prepare a dose of 0.5 mg, a volume of 0.01 mL of progesterone is drawn (calculation, 0.5 mg = 0.01 mL of 50 mg/mL solution). Because of the very small volumes involved in IM desensitization, a 1-mL TB syringe was used, and contained overfill for needle priming.

Oral capsules used in oral desensitization protocols were prepared by the BWH pharmacy by geometric dilution using microcrystalline cellulose as the diluent. Capsules were prepared in standardized incremental concentrations based on the target progestogen desensitization dose. For example, capsules for the slow oral desensitization protocol described in Table II were prepared in 1.25, 12.5, 50, and 125 µg progestin concentrations.

Patients were maintained on a total daily dose of 90 to 180 mg progesterone after IM desensitization as needed for fertility treatment depending on the specific IVF protocol as determined by the reproductive endocrinologist. For oral protocols, patients were continuously cycled on oral contraceptive pills (OCPs) at typical doses to suppress ovulation. Follow-up was conducted with patients

TABLE II. Slow oral desensitization protocol for a progestin

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, 75 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 protocol: Norethindrone 1 mg/ethinyl estradiol 0.02 mg.

TABLE III. IM progesterone desensitization protocol for IVF

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 (ie, 8% gel once or twice daily) or IM progesterone 50-75 mg daily, depending on IVF protocol

Patients were premedicated with H1 and H2 blockers, completed in outpatient infusion center with registered nurse trained in desensitization.

after progestogen desensitization to assess symptom control, fertility treatment tolerance, and pregnancies.

RESULTS

Symptom onset was classified as being triggered by endogenous progesterone or exogenous progestogen exposure (Table IV). *Endogenous progesterone triggers* were defined as menses or pregnancy without additional hormone supplementation. Endogenous progesterone levels increase during the luteal phase of the menstrual cycle, which lasts from ovulation to the onset of menses. Most patients experienced symptoms during the luteal phase of the menstrual cycle (Figure 1, A). *Exogenous progestogen triggers* were defined as symptom onset proximal to exposure to any progesterone source not naturally occurring. This includes progesterone injections or pills derived from soy, yam, or animal sources as used in IVF, as well as progestins, synthetic forms of progestogens, encompassing 21-carbon derivatives (ie, medroxyprogesterone acetate, megestrol acetate, norgestrel) and 19-nortestosterone compounds (ie, norethindrone, norethindrone acetate, levonorgestrel) commonly used as emergency contraception, OCPs, and hormonal intrauterine devices.²⁸ This population includes patients who previously tolerated menses, and in some cases pregnancy, but who developed symptoms proximal to exogenous progestogen exposure later in life. This latter group may be classified as having a “mixed” picture of PH given the initial exogenous exposure, but with similar reaction to subsequent endogenous triggers including menses and pregnancy.

TABLE IV. Classification of PH presentation

Classification	Triggers	Manifestation
Endogenous	Primary	Menses
	Pregnancy	Perimenstrual symptoms
Exogenous	Secondary	Supplemental progestogen*
	Mixed†	Supplemental progestogen*

*Includes nonnative progesterone, and progestins.

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

Characteristics of the patients in the case series sample are outlined in Table I. Age of symptom onset ranged from 13 to 48 years, with some patients becoming symptomatic at the onset of menses and other patients with symptom onset just before menopause. Women in their teens and 20s primarily reported an endogenous trigger (N = 6 of 11; 55%) and young patients represented most of the cases with endogenous triggers overall. In contrast, most patients in their 30s had symptom with exogenous progestogen exposure. Five of the 6 patients pursuing IVF were in this group.

One patient reported intrauterine device placement as her primary trigger, and 2 patients with primary endogenous triggers reported worsening of their symptoms with intrauterine device placement. The single emergency contraception (levonorgestrel) case was a patient in her 20s without previous exogenous progestogen exposure who took 1 dose of emergency contraception. OCP use was more widespread and was cited as the primary source of exogenous progestogen exposure for patients throughout the age spectrum. Two patients had carried pregnancies to term before the development of symptoms months to years after pregnancy, without additional exogenous exposures.

Seventy-five percent of the patients reported symptom onset within the week before menses (Table I; Figure 1, A). Across the sample, symptoms were primarily dermatologic including dermatitis, urticaria, and angioedema (Figure 1, B). Twelve patients had more than 1 symptom, often during the same flare. Three patients (13%) developed asthma symptoms, whereas 2 patients reported anaphylactic reactions triggered by endogenous progesterone.

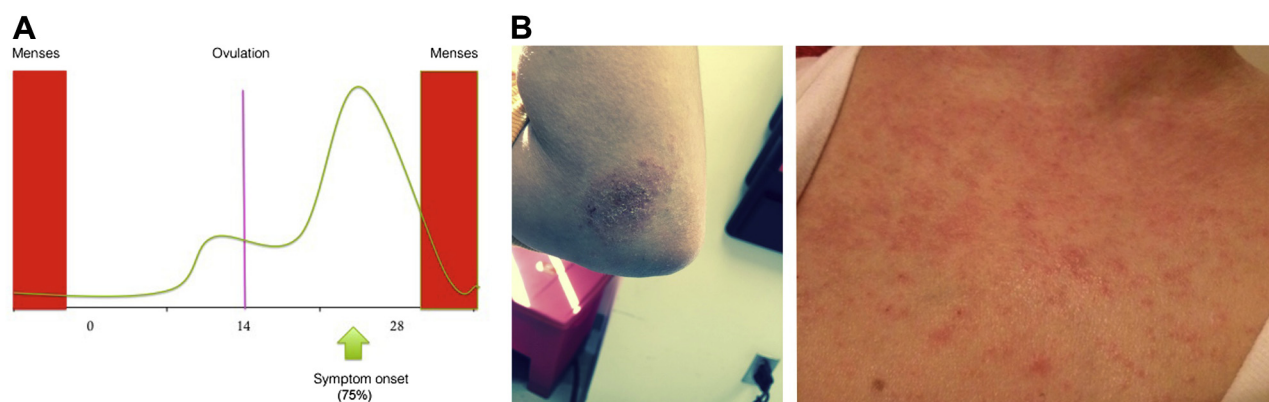


FIGURE 1. **A**, Progesterone levels during the menstrual cycle. Progesterone levels during the major phases of the menstrual cycle. *Arrow* indicates perimenstrual window for PH symptoms in most patients (75%) with endogenously triggered or mixed-picture PH. **B**, PH presenting as dermatitis. Examples of dermatitis in 2 patients with PH. Dermatitis presenting on extensor surfaces (left). Dermatitis presenting across the chest (right). Photographs used with patient permission.

TABLE V. Summary of patient management and outcomes

Strategy	Medical management (N = 13)	Desensitization (N = 11)
Method	Hormone-based therapies (54%) Nonhormonal therapies* (62%)	Oral protocol (73%) IM protocol (27%)
Outcome	Symptom improvement (92%)	Symptom improvement: dermatologic (88%); asthma/anaphylaxis (100%) Tolerating IVF (3 of 3) Pregnancy (2 of 3)

*Includes patients comanaged on OCPs.

Skin test result was positive in 50% of the patients. The remaining 50% either had a documented negative skin test result (17%) or a noninterpretable result (33%), but symptoms of PH after either exogenous or endogenous response to progestogens and symptom improvement after progestogen desensitization or suppression of the luteal phase of the menstrual cycle. The primary diluent for testing was benzyl alcohol. Three of the patients with noninterpretable or negative skin test results demonstrated respiratory symptoms or drop in FEV₁ during testing, but were not included in the skin test positive group. Patients were not blinded during testing. No oral challenges to progesterone were performed.

Of the 24 cases, 64% were managed medically for symptom relief and 46% were desensitized (Table V). Medical management included hormone-targeted therapies such as continuously cycled OCPs and leuprolide acetate. These patients often also continued to use nonhormonal therapies, primarily antihistamines, topical steroids, and montelukast, which were titrated over time to relieve symptom burden. Sixty-two percent of all medically managed patients continued to need nonhormonal therapies for symptomatic relief.

Desensitization protocols were either oral or IM (Tables II and III). The primary indication for patients who received desensitization was symptom control, including anaphylaxis. Both the patients with anaphylaxis were desensitized with an oral protocol

without complications. One patient with dermatitis symptoms failed the first slow oral desensitization but was successfully desensitized with an extended oral protocol. Three patients pursuing IVF were desensitized with an IM protocol. All tolerated IVF, resulting in 1 live birth and 1 pregnancy at the time of article submission.

DISCUSSION

The documented heterogeneity of APD is well illustrated in this case series. At present, we do not have an established mechanistic understanding about the underlying pathogenesis of APD. However, several trends emerge from this large case series that may be used to guide a differential diagnosis and decision making. These trends also suggest a need for renaming and reclassification of APD. We propose the name PH instead of APD. For many of the patients in our case series, there is no evidence of autoimmune involvement; however, all the patients demonstrate hypersensitivity to progestogen. In addition, we propose the use of the term “progestogen” rather than “progesterone” because it captures native progesterone and progestins, the synthetic progesterone-related molecules.

We also propose a classification of PH based on initial trigger of endogenous progesterone or exogenous progestogens as a practical tool for diagnosis that can be used across specialties to consistently categorize disease phenotypes (Table IV). This includes a subgroup of patients with initial symptoms triggered by exogenous progestogens, who then go on to develop perimenstrual symptoms in the absence of exogenous progestogens (mixed exogenous classification). This classification system may also facilitate earlier diagnosis by directing attention to exposures rather than symptoms. Considering endogenous progesterone exposure early in the differential diagnosis may speed diagnosis particularly in younger age groups. An alternative classification system based on the mechanism of the reaction (such as immediate or delayed) could also be considered in the future because 50% of the patients presented with positive skin test result, indicating IgE sensitization and mast cell mediator involvement. However, at this time the mechanism of the disease is not well understood and further study is needed to clarify the potential mechanisms of the different symptomatology.

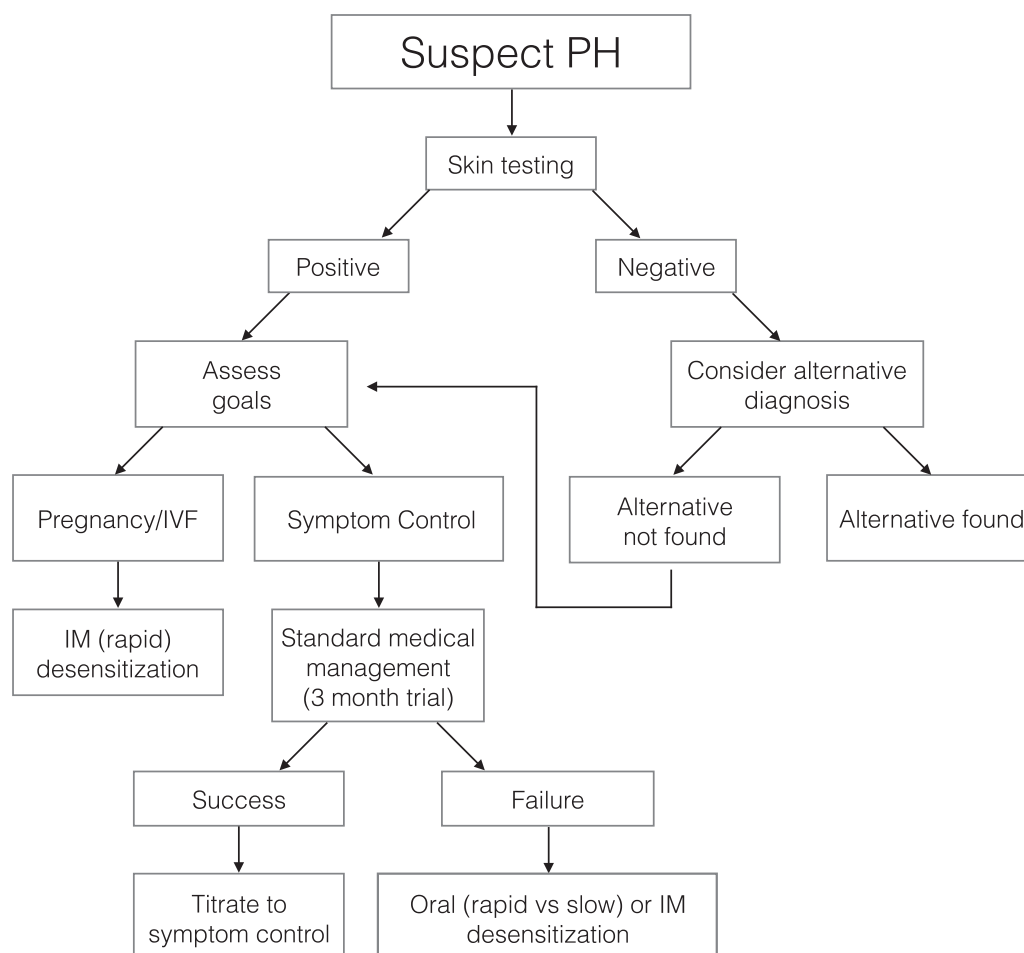


FIGURE 2. Decision tree for PH management. Framework for management of PH based on presentation, symptoms, and goals to guide diagnosis and decision making.

Women with hypersensitivity to endogenous progesterone often experience cyclical symptoms during the week before onset of menses²⁹ where progesterone levels are peaking in the luteal phase of the menstrual cycle. The luteal phase is heralded by a luteinizing hormone surge triggering follicular rupture, oocyte release, and progesterone secretion by the corpus luteum. The luteal phase almost invariably lasts 14 days, ending with the onset of menses.³⁰ Progesterone levels are low during the follicular phase of the menstrual cycle, which begins with the onset of menses, and ends the day before the luteal phase. Optimal timing for desensitization with oral and IM protocols (excluding cases in which desensitization is timed for embryo transfer or IVF) is therefore early in the follicular phase to prevent breakthrough bleeding by halting ovulation before the luteal phase (Figure 1, A).

Although only 2 patients reported previous successful pregnancies, it may be important to consider that previous pregnancies do not rule out subsequent exogenous or endogenous progestogen intolerance, and high levels of progesterone exposure during pregnancy may sensitize a patient who reacts on subsequent exposures. In contrast, initiation of IVF followed by symptoms frames exogenous progesterone as a more obvious cause of PH. However, early recognition by nonallergists, particularly

reproductive endocrinologists and gynecologists, is critical to avoid delay in diagnosis and unsuccessful IVF cycles due to difficulty tolerating supraphysiologic doses of progesterone.

All patients in our sample had skin testing to progesterone, yielding positive results in 50% of those tested. In addition, there were 3 patients with negative or uninterpretable test results who had a drop in FEV₁ during testing. Two of the 3 patients with the fall in FEV₁ had a history of anaphylaxis to progesterone. Therefore, the current skin testing protocols may not be sensitive enough to capture all sensitized patients or some reactions may reflect a different mechanism. In more recent testing protocols, an olive oil diluent has been trialed as a potentially less irritating alternative to benzyl alcohol. Olive oil, rather than sesame oil, was used for skin testing because commercial progestin products are often prepared in sesame oil and we did not want to introduce potential sesame allergy as a confounding factor. One patient in our sample was tested with this new diluent protocol; skin test result was positive. Anecdotally, experience among the authors suggests that the irritant reaction to olive oil may be just as high as with benzyl alcohol (P. G. Wickner, unpublished data, 2015). Given the high number of irritant reactions with the benzyl alcohol diluent, relative positivity was used to determine positive skin testing

results. Delayed skin test reads were not formally done for patients with late-onset, nonurticarial dermatitis to evaluate for delayed hypersensitivity. Instead, patients were asked to call the clinic to notify their physician of delayed reactions. The study of delayed skin test reads for PH is an area to be considered for future study. Furthermore, progesterone challenge was not routinely done after negative or irritant skin testing reactions because many patients did not have history of reaction to just 1 dose of progesterone and many patients developed severe rashes lasting for weeks after progesterone exposure. Under study by our group is the possible use of water-soluble depo-progestins, which would eliminate the irritant effects in current skin testing methods.

After diagnosis of PH, management and decision making are directed by patient goals and urgency of progesterone desensitization (Figure 2). For patients who require high-dose progesterone for fertility treatment/IVF, we recommend that they undergo rapid IM progesterone desensitization (Table III). This ensures that the patients will develop rapid tolerance to progesterone in an observed setting so that they are ready for embryo transfer at the appropriate time in collaboration with the reproductive endocrinologist. Of the 3 patients in this series who underwent rapid IM progesterone desensitization, all were able to tolerate IVF and 2 went on to become pregnant (Table V).

If the patient's goal is symptom control and improved quality of life, alternative medical therapies such as management of pruritus with antihistamines or suppression of ovulation with an oral contraceptive can be trialed. If the patient fails medical management after 3 months, either rapid or slow desensitization should be attempted as per the patient and allergist's preference. Of the patients who had severe symptoms refractory to standard medical therapies and underwent desensitization, almost all patients could be successfully and safely desensitized with an oral protocol (Table II). The mechanism of symptom relief in these patients is presumably suppression of ovulation by the OCP and thus a steady-state level of progesterone, rather than cycling of progesterone during the luteal phase of the menstrual cycle. Notably, the patients must continually cycle on the OCP because there is risk of resensitization within several days if the progestin is stopped to induce a withdrawal bleed during the placebo week.

Patients in this series who did not undergo progestogen desensitization experienced symptom improvement with a variety of medical therapies including high-dose antihistamines, oral and topical corticosteroids, OCPs, omalizumab, and depot leuprolide (Table V). Although 46% of medically managed patients had symptom improvement with safe and noninvasive medical interventions, other patients required medications with unacceptable long-term adverse effects (depot leuprolide or oral corticosteroids) or oophorectomy. Patients with symptoms that are not adequately controlled by safe long-term medical therapies should be offered desensitization to avoid further morbidity associated with adverse effects of steroids and leuprolide. Thirty-one percent of medically managed patients were planning to pursue desensitization at the time of article submission.

Of note, in the literature on PH, endogenous sources of progesterone, exogenous progesterone, and progestins (synthetic progestogens) are often grouped together as "progesterone." However, on a molecular level, these compounds differ. Most

clinically used progestogens are obtained by modifying the testosterone molecule to remove most of its androgen activity (ie, 19-nortestosterones).²⁸ Practically, PH symptoms that are endogenously versus exogenously triggered seem to be clinically indistinguishable. The presence of a "mixed" exogenous-type PH supports this concept because an initial exogenous progestogen trigger can later result in perimenstrual symptoms caused by endogenous progesterone. Furthermore, patients with endogenously triggered PH are desensitized to progestin compounds with symptom relief. However, the molecular difference in the compounds should remain an area of consideration for future studies.

As more patients continue to have high-dose progesterone exposure for fertility treatment or have exposure to progestin-based contraceptives, the incidence of PH will likely rise. Awareness of the PH syndrome by allergists and gynecologists, as well as primary care physicians and dermatologists, is essential to prevent delay in diagnosis and initiation of appropriate therapy. As demonstrated in this large case series, progestogen desensitization is effective in most patients, and can allow women to safely tolerate the high-dose progesterone supplementation used for early pregnancy support in IVF cycles.

Acknowledgment

We gratefully acknowledge Alicia Prieto-Garcia, MD, for the illustration used in Figure 1, A, and the permission to modify as needed.

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