

Progestogen Hypersensitivity



An Evidence-Based Approach to Diagnosis and Management in Clinical Practice

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KEYWORDS

- Progesterone • Progestin • Progestogen hypersensitivity
- Autoimmune progesterone dermatitis • Desensitization • In vitro fertilization

KEY POINTS

- Progestogen hypersensitivity (PH) may be triggered by endogenous progesterone or exogenous progestin exposure.
- The heterogeneity of progestogen exposures and PH symptoms underscore the importance of a systematic and thorough history and physical during the patient encounter.
- Current skin-testing methods for PH yield equivocal results and is an active area of research.
- Patient-specific symptom profiles and patient goals should guide treatment.
- Desensitization to progestogens has been demonstrated as a safe, reproducible option for women pursuing pregnancy through in vitro fertilization as well as for refractory symptoms.

INTRODUCTION

Although the term progestogen hypersensitivity (PH) is a relatively new addition to the allergy/immunologist lexicon,¹ progesterone hypersensitivity syndromes were first described more than 50 years ago.² In the intervening years, the term autoimmune progesterone dermatitis was a common reference to a heterogeneous collection of symptoms. However, as recent studies have demonstrated, there is little evidence

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supporting an autoimmune pathophysiology, and the range of PH symptoms include both immediate and delayed-type hypersensitivity. This article reviews a systematic approach to patient diagnosis, centered on a triad of history, physical examination, and testing. This approach will then form the basis for a discussion of current evidence on treatment strategies, including desensitization and longitudinal symptom management.

DEFINITIONS

Progestogen describes a group of steroid hormones that includes both progesterone and progestins.

Progesterone is an endogenously synthesized hormone derived from cholesterol. The roles of progesterone in obstetrics and gynecology has been well defined, particularly in its role as a mediator of the menstrual cycle. Levels rise in the luteal phase, and fall in the follicular phase, leading to menstruation.^{3,4} In pregnancy, progesterone is produced by the corpus luteum and then the placenta.^{5,6} Progesterone has also been implicated in endocrine signaling to a variety of other organs including the brain and lungs.⁷ Investigating progesterone's role in sex differences in common diseases, such as asthma, is an active area of research without conclusive evidence to whether it mitigates or facilitates respiratory inflammation.^{8,9}

Progestins are synthetically derived by editing side chains on a different group of hormones, primarily 19-nortestosterone, 17 α -hydroxyprogesterone or acetoxyprogesterin.¹⁰ Therefore, oral and implantable contraceptives and intrauterine devices (IUDs) are composed of a distinctly different chemical structure than endogenous progesterone, yet still fall under the rubric of progestogens.

EPIDEMIOLOGY

Despite its description more than 50 years ago, the prevalence of PH remains unknown. Women between menarche and menopause can be affected, with the average age of onset to be in the third decade of life, with a mean age of 27.3 years (range 12–47) and 29.7 years (range 13–48) in 2 different studies.^{1,11} A single case report of hypersensitivity to progestin has been reported in a man, who reacted to megestrol acetate and confirmed by positive skin testing to progesterone acetate.¹²

THE CLINICAL ENCOUNTER

The history and physical is an essential starting point for the diagnosis of PH, as outlined in [Table 1](#).

History

The heterogeneity of progestogen exposures and PH symptoms underscores the importance of a systematic and thorough history and physical during the patient encounter. A classification schema for PH presentation has been previously proposed ([Table 2](#)).

Progestogen hypersensitivity from endogenous progesterone exposure generally correlates with monthly symptoms that occur 3 to 10 days before the onset of menses ([Fig. 1](#)). However, as in the general population, some women with PH may have metrorrhagia and experience PH at other intervals. These symptoms may remit at menopause or may persist.^{13,14} Keeping a menstrual diary of symptoms may help identify symptoms correlating with each period, albeit irregular in timing. The pattern of PH in pregnancy and its natural history is not well documented, as intrapartum

Table 1
Key elements of the history and physical examination for PH diagnosis

Clinical Encounter	Area of Focus	Key Findings
History	Symptom timing OB-GYN history	• Cyclical pattern • Menses • Pregnancies and terminations • Assisted fertility
	Medication use	• Progestogens • NSAIDs
Physical	Dermatologic	• Rash • Urticaria • Angioedema
	Pulmonary	• Wheezes
	Pelvic	• Pruritus • Labial swelling

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; OB-GYN, obstetrics-gynecology; PH, progesterone hypersensitivity.

improvement has been reported.¹⁵ In other case reports, patients have developed symptoms during pregnancy and postpartum.^{16–22} Patients may have previously tolerated menses but develop cyclical symptoms later in life following endogenous (ie, pregnancy) or exogenous progesterone exposure. Nguyen and Razzaque Ahmed¹¹ found that 40 (44.94%) of the 89 cases they reviewed had known prior exposure to exogenous progesterone. Of note, family history of PH is not thought to be a risk factor, but there is one case report of 3 sisters with PH.²³

Exogenous sources of progesterone are an important and growing consideration in PH diagnosis and successful management. Sources include progestins in oral contraceptive pills (OCPs),^{14,20,24} long-acting depot preparations such as

Table 2
Classification of progesterone hypersensitivity presentation

Exposure Classification	Trigger	Timing
Endogenous		
Primary	Menses Pregnancy	Perimenstrual symptoms Monthly symptoms after completion of non-in vitro fertilization pregnancy
Exogenous		
Secondary	Supplemental progesterone ^a	Symptoms only during supplemental progesterone administration
Mixed ^b	Supplemental progesterone ^a	Took supplemental progesterone, then develops perimenstrual symptoms

^a Includes synthetic progesterone and progestins.

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

Adapted from Foer D, Buchheit KM, Gargiulo AR, et al. Progesterone hypersensitivity in 24 cases: diagnosis, management, and proposed renaming and classification. *J Allergy Clin Immunol Pract* 2016;4(4):725; with permission.

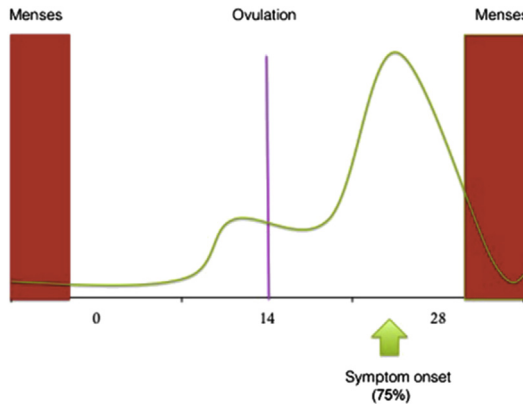


Fig. 1. Progesterone levels during the menstrual cycle. (From Foer D, Buchheit KM, Gargiulo AR, et al. Progesterone hypersensitivity in 24 cases: diagnosis, management, and proposed renaming and classification. *J Allergy Clin Immunol Pract* 2016;4(4):726; with permission.)

medroxyprogesterone acetate,^{3,22,25} vaginal rings,²⁶ emergency contraception, and IUDs.¹ The rise of in vitro fertilization (IVF) and use of high-dose progesterone is now well documented as an emerging source of PH and a further barrier to achieving pregnancy using assisted reproductive technologies.²⁰ Of note, there are no published cases of PH secondary to hormone replacement therapy, although the diagnosis

Therefore, on history, 2 questions can help guide diagnosis of PH: What is the presumed progestogen exposure, and what is the timing of patient symptoms? Taken together, these can help the clinician avoid common diagnostic delays.^{3,24}

should be considered in the differential with a suggestive history and physical.

Physical

Patients may present with active physical manifestations of PH, photos of past flares, or asymptotically based on symptom timing. Dermatologic findings are most common and include a broad range of pathology, including urticaria with or without angioedema,^{3,21,27–30} eczematous dermatitis,^{20,31} maculopapular rash, vesiculobulbous and vesiculopustular lesions,^{2,15,24} petechiae and purpura,^{32,33} fixed drug eruption,^{34,35} stomatitis,^{36,37} and erythema multiforme.^{19,38} Some of these findings may be localized to the pelvic area, including vulvovaginal pruritus,³⁹ and labial swelling.⁴⁰ Respiratory symptoms, such as asthma, have been reported and there are also reports of anaphylaxis^{14,21,25,34,41}; in some patients both dermatologic and nondermatologic manifestations have been described.^{14,34,38,42}

Following the clinical encounter, the differential diagnosis for PH includes other steroid-based syndromes, medication triggers other than progestogens, and a variety of primary dermatologic pathologies (Table 3). Of note, eliciting a thorough medication history is important in differentiating PH from other immediate or delayed-type hypersensitivity syndromes.

Table 3
Differential diagnosis for progesterone hypersensitivity

Medications	Particularly nonsteroidal anti-inflammatory drugs, commonly used in premenstrual period ²⁶
Primary dermatologic pathology	Chronic idiopathic urticaria, atopic dermatitis, allergic contact dermatitis
Steroid hypersensitivity syndromes	
Catamenial anaphylaxis	Symptoms correlate with ONSET of menstrual cycle ⁴³
Estrogen hypersensitivity	Exogenous or endogenous estrogen leads to premenstrual urticaria or delayed-type dermatitis with positive estrogen skin test ⁴³⁻⁴⁷
Lactation anaphylaxis	Clinical correlation with breastfeeding or manual expression of breast milk ⁴⁸⁻⁵³

DIAGNOSTIC TESTING OPTIONS

Common diagnostic modalities in clinical practice include progesterone skin testing and challenge.^{29,30,54} However, the equivocal results from current skin-testing methodologies discussed as follows highlight the importance of a convincing clinical history in making the diagnosis of PH.

Skin Testing

Skin prick testing is conducted with progesterone (50 mg/mL) in serial dilutions. Diluents can be ethanol or oil based. False-positive reactions caused benzyl alcohol or oil-based diluents have been described.¹ Wheal and flare are compared with diluent (either oil or ethanol) and positive histamine controls.^{1,29,55} Testing with water-soluble progestins has been proposed as an alternative to progesterone skin testing. However, similar limitations exist given additives to progestins such as polyethylene glycol, which can also cause irritant reactions.^{54,56} 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.¹ In a recent study of 24 patients with clinical history consistent with PH, only 50% of patients had positive progesterone skin testing. This included patients with observed respiratory symptoms during skin testing, but negative skin test results. Therefore, the positive predictive value and negative predictive value of skin testing is unknown and cannot alone rule in or rule out PH.

Progesterone Challenge

The utility of progesterone challenge is limited in the diagnosis of PH. A clear history of symptoms following exogenous progesterone exposure may obviate the need for further progesterone challenge. Risks of challenge include symptom exacerbation.^{2,19} Rather than challenge, empiric treatment focused on patient symptoms or desensitization may be an appropriate next step (Fig. 2).

Patch Testing

Attempts at progesterone patch testing have not been shown to be a more useful diagnostic tool than existing modalities.⁵⁵ This is a potential area for further investigation, as patch testing is an attractive method for testing for delayed-type hypersensitivity reactions.

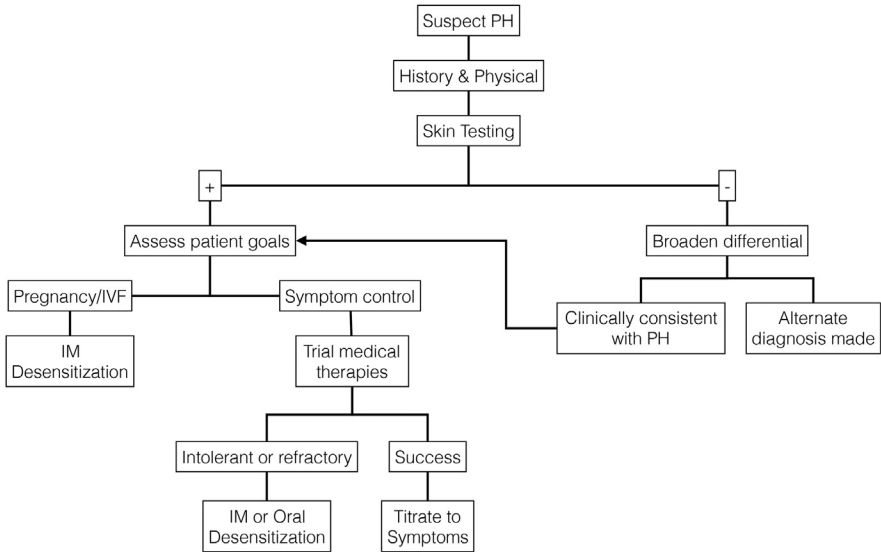


Fig. 2. Management tool for PH to guide diagnosis and treatment. (Adapted from Foer D, Buchheit KM, Gargiulo AR, et al. Progesterone hypersensitivity in 24 cases: diagnosis, management, and proposed renaming and classification. *J Allergy Clin Immunol Pract* 2016;4(4):727; with permission.)

Precision diagnostic testing is an active area of research, as discussed later in this article.

MANAGEMENT

Management of PH is directed by the severity of patient symptoms and patient goals, as outlined in [Fig. 2](#). Interestingly, the specific progestogen trigger does not seem to matter in terms of responsiveness to medical management and treatment with desensitization.^{2,13,17}

[Table 4](#) outlines current treatment options for PH. Medical management with antihistamines or topical or oral corticosteroids can be initially trialed for patients desiring symptom control.^{21,41,42,57} Tolerance of these therapies is variable, and often limited by adverse side effects for long-term use. Three months has been suggested as a reasonable trial period for medication management, although this may be at the discretion of the patient and clinician. Patients who do not respond to symptom management may require suppression of ovulation or desensitization as described in the following paragraph.

Suppression of ovulation with OCPs can control symptoms in many patients. However, some patients cannot tolerate the low-dose progestin in OCPs and instead require treatments with other medications that suppress ovulation, such as gonadotropin-releasing hormone (GnRH) agonists,^{3,14,22,41,58,59} alkylated androgens,^{50,59} and tamoxifen.^{4,19,37} However, symptoms of hypoestrogenemia with GnRH agonists and tamoxifen, and androgen-induced side effects with the 17- α -alkylated steroids severely limit their use. Oophorectomy remains a definitive, curative option for PH of endogenous or mixed etiology, although should be considered only in refractory cases or based on patient preference.^{2,36,60,61}

Table 4
Treatment options in progestogen hypersensitivity

Treatment Category	Drug Class	Potential Benefits	Potential Limitations
Symptomatic relief	Oral antihistamines	Acute relief of itching, swelling	Incomplete efficacy
	Topical glucocorticoids	Acute relief of itching, swelling	Incomplete efficacy, long-term side effects
	Systemic glucocorticoids	Acute relief of itching, swelling, wheezing	Incomplete efficacy, long-term side effects
Ovulation suppression	Combined oral contraceptive pills	Readily available	Possible hypersensitivity reaction to low-dose progestin ^a
	GnRH agonists	Alternative if unable to tolerate OCPs	Estrogen withdrawal symptoms including bone loss, hot flashes, urogenital atrophy
	Selective estrogen-receptor modulators	Alternative if unable to tolerate OCPs	Estrogen withdrawal symptoms including bone loss, hot flashes, urogenital atrophy
	17- α -alkylated steroids	Alternative if unable to tolerate OCPs	Hirsutism, mood changes, LFT abnormalities
	Oophorectomy	Definitive symptoms relief in cases of endogenous PH	Premature menopause, permanent loss of fertility
Desensitization	Rapid desensitization to IM or intravaginal progestogens	Can be precisely timed to IVF needs; enables successful pregnancy	Resource intensive, risk of hypersensitivity reactions during desensitization
	Rapid or slow desensitization to oral progestins	Can be tailored to goal dose of progestin; long-term symptom control	Risk of hypersensitivity reactions during desensitization; long-term cycling on hormones to avoid resensitization

Abbreviations: GnRH, gonadotropin-releasing hormone; IM, intramuscular; IVF, invitro fertilization; LFT, liver function tests; OCPs, oral contraceptive pills; PH, progestogen hypersensitivity.

^a Desensitization to OCPs is an option for managing this side effect.¹

For patients undergoing fertility treatment/IVF requiring high-dose progesterone, symptom management described previously is not an option. In these cases, progesterone desensitization has been shown to be a successful, reproducible modality for treatment, allowing patients to tolerate high-dose progesterone required to maintain pregnancy. Although intramuscular (IM) and vaginal protocols appear to have equal efficacy, IM has been recommended as the easiest modality for rapid desensitization.^{2,12,13} The timing of desensitization relative to embryo transfer is determined in collaboration with a reproductive endocrinologist.

The success and safety of desensitization to date positions it as an option to more readily consider in cases outside the IVF realm. Indications include severe symptoms not optimally controlled with symptom-focused medications.^{2,36,60,61} In these cases, a rapid or slow oral desensitization protocol may be used. The protocols have been detailed elsewhere in the literature.^{2,13} Following desensitization, patients must continually cycle on the OCP to maintain a steady state of progesterone to avoid resensitization.

ACTIVE AREAS OF RESEARCH

Pathomechanisms of Progesterone Hypersensitivity

The underlying cause of PH is unknown. It has been theorized that patients with PH are sensitized via exposure to exogenous progesterone and progestins used for either contraception or fertility treatments.⁶² However, as described previously, only half of patients with PH have history of prior exposure to progestogens.¹¹ An alternative mechanism by which patients may become sensitized to progestogens is cross-sensitization to related corticosteroids.⁶³ Regardless of the cause of PH, it appears that multiple mechanisms may be at play given the wide variety of clinical manifestations that can occur in PH. Proposed mechanisms include mast-cell activation⁶⁴ and immune complex deposition.^{19,65}

Advances in Diagnostic Testing

Given the problems with progestogen skin testing described previously, development of more accurate in vitro tests would greatly assist the allergist in diagnosing PH. Several experimental tests have been used to diagnose PH. A direct leukocyte histamine release assay and a progesterone-specific immunoglobulin (Ig)E enzyme-linked immunosorbent assay have been used by Bernstein and colleagues.¹⁴ An assay to detect interferon-gamma release also has been proposed.⁶⁶

Potential Treatment Options

Omalizumab, a monoclonal antibody directed against IgE, was used to treat a patient with cyclic episodes of anaphylaxis, not responsive to antihistamines and oral corticosteroids, and positive skin testing to progesterone. Resolution of the recurrent episodes of anaphylaxis occurred quickly and the patient tolerated the treatment well.⁴⁰ Omalizumab may represent an excellent choice for patients with PH who develop urticaria and anaphylaxis. It is not clear that this treatment will be helpful to patients with more delayed-type reactions and is an area for further study.

SUMMARY

PH manifests as a wide variety of hypersensitivity reactions and can occur with endogenous or exogenous progestogen exposure. The allergist/immunologist is uniquely suited to diagnose and treat PH. A careful clinical history and identification of

progesterone as a trigger is paramount to the diagnosis of PH. Patient-specific symptom profiles and patient goals should guide treatment.

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