



Progestogen Sensitization: a Unique Female Presentation of Anaphylaxis

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Abstract

Purpose of Review Progestogen hypersensitivity (PH) is a condition which typically occurs in women in childbearing years with a spectrum of symptoms ranging from urticaria with or without angioedema, dermatitis to systemic anaphylaxis. Herein, a clinical case of PH is presented followed by a discussion on the evaluation, diagnosis, and management of PH.

Recent Findings Progestogen hypersensitivity (a.k.a. “autoimmune progesterone dermatitis”) symptoms are associated with exogenous progestin exposure (e.g., contraceptive medicines, in vitro fertilization therapy) or endogenous progesterone from progesterone surges during the luteal phase of the menstrual cycle and pregnancy. This condition can be difficult to recognize due to its heterogeneous clinical presentation. The mechanism of PH is believed to be primarily IgE-mediated; however, less commonly other immune responses may be involved. There is now a useful progesterone specific IgE immunoassay to assist in diagnosis and well-defined treatment algorithms that can be used to successfully manage PH.

Summary The epidemiology of PH is still poorly elucidated but is likely to be encountered by clinicians and especially allergists given the extensive use of oral contraceptives and increased use of supra-physiologic doses of progesterone required to support pregnancy in IVF. Including PH in the differential diagnosis of women presenting with cyclic hypersensitivity will accelerate diagnosis and successful management of this condition.

Keywords Progestogen hypersensitivity · Autoimmune progesterone dermatitis · Desensitization · Diagnosis and treatment · Clinical characteristics · Case presentation

Case Presentation

A 23-year-old female presents with concerns about possible mast cell activation syndrome. She started to have clinical symptoms at around age 17 of hives associated with tongue swelling. The episode originally began while she was taking a sulfonamide antibiotic for a sinus infection, but symptoms persisted after discontinuation. Treatment with diphenhydramine and oral glucocorticoids provided relief but they reoccurred with discontinuation. The hives involved approximately 20% of her body, mainly occurring on her chest and arms and were very pruritic.

She had associated fatigue and was previously diagnosed with fibromyalgia. Of note, she had an IUD and gets symptoms of a period but no menstrual flow. The hives appeared to occur certain times of the month but she had not been tracking this with any regularity. They also seemed to be worse with heat. She has no history of asthma but has been evaluated by a previous allergist and was diagnosed with seasonal allergic rhinitis to ragweed. She has no history of hypermobility or other features of dysautonomia although she endorses heart racing when she gets nervous. During her initial visit, she was started on high-dose second-generation antihistamines, an H₂ antihistamine and a leukotriene receptor antagonist. In addition, a CBC with differential, sedimentation rate, C-reactive protein and thyroid stimulating hormone as well as biomarkers for mast cell activation syndrome including serum tryptase, 24-h urine for methylhistamine and prostaglandin F₂α were ordered. On follow-up 6 weeks later, she was still experiencing hives that were difficult to determine if they were associated with her menstrual cycle. Her laboratory testing was completely negative. The patient was advised that PH could be a contributing factor and that removing her IUD would

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help in making this diagnosis. In addition, a test that measures sIgE to progesterone was ordered. Treatment with omalizumab to control her persistent chronic urticaria was also discussed. Three months later, the patient returned for follow-up. She had her IUD removed and was now able to determine the cyclic nature of the recurrent hives around her menstrual cycle. Her specific IgE to progesterone was positive. Omalizumab was started to control the hives followed by oral progesterone desensitization.

Introduction

Progestogen hypersensitivity (PH), (a.k.a. autoimmune progesterone dermatitis or APD) was first described in 1964 [1]. Symptoms were noted as a pruritic, clustered, vesicular skin rash but rashes have been reported to vary from plaques, urticaria with or without angioedema, eczema, fixed drug eruptions, and erythema multiforme [1–17]. Some patients have been reported to experience systemic symptoms including wheezing, shortness of breath, chest tightness, and anaphylaxis [4, 9, 13, 18, 19]. The condition was initially postulated to be an autoimmune disorder triggered by endogenous progesterone [1]. However, there has been little evidence to support an autoimmune mechanism of action and evidence now supports that this is an IgE-mediated hypersensitivity reaction to progesterone [20–22, 23•]. The term “progestogen” hypersensitivity is used rather than “progesterone” as it encompasses both natural progesterones and synthetic progestins [21]. The use of the term “progestogen” is a recently introduced neologism and most medical literature still uses other terms like APD. It is also worth noting that there is an ICD-10 code for APD but none exists for progestogen hypersensitivity.

Progestogen hypersensitivity is a form of cyclical hypersensitivity that affects women of childbearing age with symptoms beginning between menarche and menopause [24•]. Reviews of large case series report a mean age of onset at approximately 28 years (range 12 and 48 years) [12, 22, 24•]. Women typically have a history of current or prior exogenous progesterone exposure which may be a risk factor; however, some cases have reported women with PH who experienced symptoms without prior exogenous progesterone exposure but symptom correlation with endogenous progesterone exposure during menses or pregnancy [2, 5, 12].

The epidemiology of PH is unknown but may be more common than realized although, however, its exact prevalence is unknown [21, 23•, 25].

Mechanism of Action

The most commonly accepted mechanism for PH is IgE-mediated sensitization to progestogen which occurs in response to an exogenous progestogen-related product. When

susceptible patients are later exposed to progestins, clinical hypersensitivity reactions occur due to cross-reactive antigenic peptides activating mast cells by cross-linking to specific IgE bound to high affinity IgE receptors on mast cells [19, 23•, 26]. A recent assay was developed to measure specific IgE (sIgE) to progesterone in women suspected of PH confirmed by a functional basophil histamine release assay that supports an IgE-mediated mechanism for PH [27•].

Delayed hypersensitivity responses have also been implicated in some PH cases as studies have demonstrated that progesterone can modulate T_H2 cells via G protein-coupled receptors [28]. In addition, it has been postulated that reactions may occur through activation of a progesterone membrane receptor α (PHR α) on CD8+ cells [28, 29]. An immune complex-mediated mechanism has also been proposed as one case report identified 17-hydroxyprogesterone-binding IgG immunoglobulin in a patient's serum experiencing cyclical perineal rashes [23•, 30]. Another case reported a woman experiencing cyclic erythema multiforme corresponding to the luteal phase of her menstrual cycle who had measurable serum immune complexes after a medroxyprogesterone challenge [17].

A less popular proposed mechanism for PH is progestogen sensitization developing after glucocorticoid exposure as they share a similar chemical structure. Evidence against this hypothesis is that numerous case studies of PH have reported successful treatment with glucocorticoids [2, 10, 17, 30, 31].

Diagnosis

The diagnosis of PH is primarily made by history confirming symptoms that are temporally related to perimenstrual progesterone surges or exogenous progestogen exposure. The history can sometimes be confusing especially in women with an irregular menstrual cycle due to underlying conditions such as endometriosis. Until recently, intracutaneous progesterone skin testing was used to assess the presence of progesterone specific IgE [23•, 25]. Skin prick testing is performed to the neat concentration of progesterone 50 mg/mL in oil. If negative, this is followed by intracutaneous testing beginning at a 0.01% dilution and increasing up to a maximum 1% dilution from the progesterone 50 mg/mL concentration in conjunction with negative diluent and positive histamine controls [8, 21, 32]. However, because progesterone is not water-soluble and requires dilution in oil or ethanol, skin testing can induce irritant reactions at high progesterone concentrations which have limited its use as a diagnostic test.

Oral graded challenges to progesterone which frequently require multiple updosings to elicit a reaction have been used but can result in severe and prolonged cutaneous outbreaks in some individuals and therefore should be used cautiously in patients with a good history of progesterone-induced

reactions. Others have suggested a graded intramuscular challenge using progesterone concentrations from 12.5 to 25 mg as an alternative diagnostic test but this approach is not very well tolerated by patients due to injection site pain [23•, 25]. Progesterone patch testing has also been used to assess for a cell-mediated immune response but has been proven to be unreliable [32].

In vitro assays have been used to investigate PH including an enzyme-linked immunosorbent assay (ELISA) to assess for progesterone specific IgE (sIgE), a leukocyte histamine release assay (LHR) to assess basophil histamine release and an interferon-gamma release assay to assess T cell-mediated activity related to progesterone [4•, 27•, 32, 33]. This later in vitro study demonstrates a cell-mediated immune response with a T_H1 -type cytokine release pattern but remains experimental. This approach would be more appropriate for assessing women presenting with cyclical chronic dermatitis reactions [33].

The LHR functional assay uses basophils incubated with serum from sIgE-sensitized patients to assess histamine release, but this test is labor-intensive and not practical for routine clinical use [4•, 27•].

An ELISA developed by Ghosh et.al. which measures progesterone serum specific IgE, is easy to perform and correlates very well with patient history and response to treatment [27•]. This ELISA test used a well-characterized progesterone bovine serum albumin (BSA) conjugate to analyze sera collected from women with suspected PH to establish high, low, and negative cut-points for the assay [27•]. Sera from healthy nonatopic female subjects were used as negative controls, and women with classical PH symptoms previously identified to have high progesterone sIgE were used as positive controls. A positive result was defined as exceeding the average negative control OD + 3 standard deviations [27•]. These cut-points were subsequently used to establish positive and negative results for sera collected from women with suspected PH received from centers around the USA [27•]. In addition, a subset of high positive sera was used for ELISA inhibition to demonstrate specificity of the ELISA assay and a rat basophil leukemic cell line to measure beta-hexosaminidase mediator release assay was used to evaluate the functional relevance of positive progesterone sIgE compared to negative sIgE tests [27•]. Using the basophil histamine release assay as the gold standard confirming the functional relevance of a positive sIgE ELISA assay, it was determined that the progesterone sIgE ELISA had a sensitivity of 82%, a specificity of 100%, a positive predictive value of 86%, and a negative predictive value of 100% [27•]. As mentioned, progesterone skin testing is unreliable. One study found that only 12 out of 24 patients with PH symptoms elicited a positive progesterone skin test [21]. The unreliability of progesterone skin testing emphasizes the importance of having a reliable serologic test. Efforts to commercialize an ELISA test so it is more readily available to clinicians are underway.

Currently, if a patient's presentation is consistent with PH and has negative progesterone skin testing and obtaining a serum sIgE progesterone test is not possible, then using medications that suppress ovulation such as oral contraceptives (OCPs) or GnRH agonists can serve as a diagnostic/therapeutic approach for confirming the diagnosis. Previous case studies using this approach have found that GnRH agonists provide better symptom control than OCPs [3, 4•, 18, 34–36]. The length of treatment with a GnRH agonist is necessary to determine symptom relief and confirm a diagnosis but should be ascertainable within 3 months, the duration of one depo injection. Fig. 1 illustrates an algorithm for the evaluation and management of PH [21].

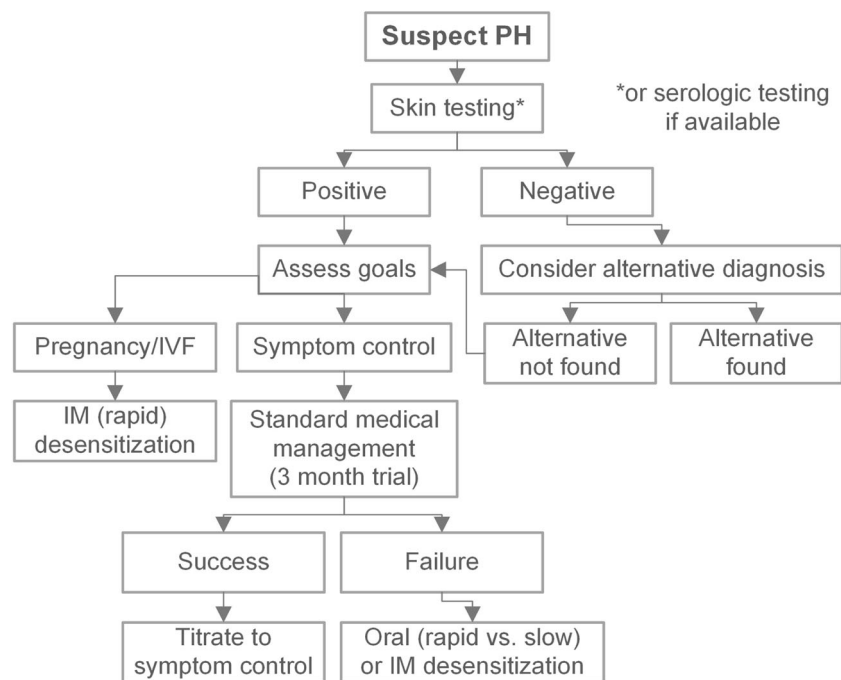
Treatment

Once a diagnosis of PH has been established, which includes symptoms of cyclic urticaria or other skin rashes and systemic symptoms, an algorithmic approach for treatment similar to what is recommended for chronic urticaria should be undertaken. Initial treatment should begin with second-generation H1-antagonist and if not effective it should be increased up to four times the FDA-recommended dose, similar to what is recommended by the US Joint Task Force Guidelines and International Chronic Urticaria Guidelines [37–39]. Adding an H2-antagonist and/or a leukotriene modifying agent to this regimen is safe and may be effective in select cases [39]. However, oral H1-antagonists are frequently not very effective for controlling PH [40]. A course of oral glucocorticoids may be effective at controlling a severe outbreak but is not recommended for long-term use based on their underlying side effects [2, 10, 30]. In some cases, if tolerated, using OCPs may be effective by inhibiting ovulation and preventing progesterone surges during the luteal phase of the menstrual cycle [35].

Both intramuscular and intranasal GnRH agonists, which suppress ovulation by inhibiting gonadotropin release from the pituitary gland and a subsequent surge in progesterone, have been used to successfully treat PH [3, 4•, 18, 34–36]. However, adverse side effects associated with this treatment, which include amenorrhea, vaginal atrophy and osteoporosis, make it less desirable for use as a long-term treatment option. Furthermore, it is frequently difficult to get this treatment approved by insurance and prior authorization is usually required.

Tamoxifen, an estrogen receptor modulator, also suppresses ovulation and has been previously used to treat PH [17, 22, 41]. However, similar to GnRH inhibitors, tamoxifen has the potential for severe long-term side effects such as osteoporosis. In addition, the 17- α -alkylated mineralocorticoids have been used to treat PH but are also associated with a number of adverse side effects including mood changes, hirsutism, masculinization, increased liver enzymes, and fatty liver [40, 42]. The most drastic

Fig. 1 An algorithm of diagnostic and treatment approach for progesterone hypersensitivity [23]. *Standard medical management: would include H1/H2 antagonists, leukotriene antagonists, OCPs, GnRH agonists, or omalizumab



treatment approach has been oophorectomy; however, this is not a practical option for women in their childbearing years who wish to have children and because of the significant increased risk of osteoporosis [1, 15, 43].

The recent approval of omalizumab, an anti-IgE monoclonal antibody, for the use of chronic urticaria not responsive to H1-antagonists, has also been used successfully to treat PH patients experiencing cyclic urticaria with angioedema and other systemic anaphylactic symptoms [44•]. In some scenarios, omalizumab can be started before progesterone desensitization and once the woman has achieved a tolerated daily dose of progesterone, it can be safely discontinued.

There are now many reported cases of successful outcomes with progesterone desensitization. Progesterone desensitization is indicated for patients with uncontrolled cutaneous symptoms despite treatment with other therapies discussed

above and/or for the need to discontinue treatments like GnRH agonist therapy to prevent long-term side effects. It has also been used for patients with PH undergoing IVF which requires high doses of progesterone for successful implantation [8, 13, 14, 21, 23•].

Progesterone desensitization likely works in a similar manner to other forms of allergen immunotherapy, but its mechanism of action has not been adequately investigated. There are several protocols that have been used depending on the patient's reaction severity and clinical requirements which are summarized in Tables 1–3, and include oral, intramuscular (IM), and intravaginal suppository protocols. The oral protocol is the preferred regimen as it is easier and safer to administer [13, 14, 23•]. Depending on the patient, the oral protocol may have to be modified to build up much slower than what is recommended to prevent breakthrough symptoms.

Table 1 Oral and intramuscular progestin desensitization protocols. Nine-day oral protocol

Day	Dose (based on progestin component)	Number of capsules × capsules 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 × 1.25 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

Table 2 Oral and intramuscular progestin desensitization protocols. Two-day oral protocol

Time (h)	Dose
00:00 (first day)	0.1 mg
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

A rapid IM protocol has previously been used successfully in patients undergoing or IVF treatment for infertility. This protocol is strongly recommended for patients undergoing in vitro fertilization because patients can quickly develop tolerance to high levels of progesterone necessary for facilitating embryo transfer in a timely manner [21, 23•]. This protocol is performed over 2.5 h and reaches a daily target dose of 50–75-mg progesterone-administered IM. The intravaginal protocol reaches a 90–180-mg progesterone dosed once or twice daily [21, 23•].

Conclusion

Progesterone hypersensitivity is the most common cause of cyclical hypersensitivity. Although the true prevalence of this condition is unknown, it is likely more common than recognized. A history of urticaria or other cutaneous eruptions with or without systemic manifestations beginning 3–10 days before the menstrual cycle that persists several days into menses or until completion suggests a diagnosis of PH. Limited availability of reliable in vivo skin tests makes confirmation by this approach challenging; however, the development of a recent ELISA test for sIgE to progesterone with high specificity and sensitivity should help facilitate a clear diagnosis of this

Table 3 Oral and intramuscular progestin desensitization protocols. Rapid intramuscular protocol for in vitro fertilization

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

condition. A therapeutic response with either OCPs, if tolerated or a GnRH agonist is confirmatory for the diagnosis of PH. Oral progesterone desensitization is the recommended treatment approach as it appears to be safe and effective. The clinician and especially the allergist should incorporate questions about cyclic hypersensitivity and specifically PH in their history for any menstruating female presenting with chronic urticaria. In cases of women with PH and infertility, the allergist immunologist will be called up to collaborate with gynecologists and reproductive endocrinologists to help diagnose and treat this condition.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations PH, Progesterone hypersensitivity; OCP, Oral contraceptive pills; sIgE, Specific immunoglobulin E; ELISA, Enzyme-linked immunosorbent assay; LHR, Leukocyte histamine release; IVF, In vitro fertilization

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