Progestogen Hypersensitivity: Heterogeneous Manifestations with a Common Trigger

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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.

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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 1964[1] 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

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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- Progestogen 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 acetoxyprogestin.[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 (ERα and ERβ) and progesterone (PRA and PRB) receptors on human, mouse, and rat mast cells (MCs).[5] In humans, mRNA expression of ERα but not ERβ has been demonstrated on MCs.[5,6] Furthermore, it has been shown that 17β-estradiol resulted in rapid MC activation that was inhibited by the ER antagonist, tamoxifen. Of importance, bone marrow-derived MCs isolated from an ERα knockout mouse did not degranulate in response to 17β-estradiol treatment indicating that the 17β-estradiol effect on MCs is mediated through the ERα 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