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 supporting an autoimmune pathophysiology, and the range of PH symptoms include

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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 acetoxyprogestin.[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 remiss 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 improvement has been reported.[15] In other case reports, patients have developed