Review Article

Exogenous Progestogen Hypersensitivity and its Increasing Association with Assisted Reproductive Techniques (ART)/*in vitro* Fertilization (IVF)

Abstract

Progestogen hypersensitivity (PH) also known as autoimmune progesterone dermatitis is a rare clinical entity that may be triggered by endogenous progesterone (menstrual cycles and pregnancy) or exogenous progestin exposure (examples: contraceptive medicines, *in vitro* fertilization treatments). It is a poorly recognized syndrome due to its heterogeneous clinical presentation. The pathomechanism of PH is believed to be primarily IgE mediated but less commonly other immune responses may be involved. Management is usually focused on symptomatic control with medications. Recently, with the increasing use of exogenous progestins for *in vitro* fertilization more cases of hypersensitivity to exogenous progestins have been reported. Progesterone is an essential drug in the luteal phase support improving chances of implantation and pregnancy rates, and hence, PH is an important and difficult challenge to manage in these patients. Because patients require IVF and there is no alternative to progesterone, desensitization is suggested as an approach to endure fertility treatments and provides symptom control in refractory cases. Here, we will review the different aspects of PH.

Keywords: *Autoimmune progesterone dermatitis, desensitization, in vitro fertilization, progesterone, progestogen hypersensitivity*

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Introduction

Progesterone dermatitis was first described by Shelley *et al*. in 1964 under the terminology "autoimmune progesterone dermatitis" (APD) as these patients reacted to endogenous progesterone.[1] However, there is little evidence to support an autoimmune pathophysiology, and the term APD does not accurately represent the condition. Therefore, Foer *et al*. proposed the name Progestogen hypersensitivity (PH), to depict a rare hypersensitivity reaction to endogenous or exogenous progesterone depending on the route of progesterone exposure as elaborated in Table 1.[2]

Endogenous PH is characterized by periodic skin rashes during the menstrual luteal phase. Exogenous progesterone's are increasingly used for assisted reproductive techniques (ARTs) for infertility or prevention of abortion, and cases of dermatitis due to administration of supraphysiological doses of exogenous progesterone have been increasingly reported.[2-5] However, while literature is available on endogenous PH, exogenous PH has not been widely reported. Hence, we decided to review this topic.

With a high prevalence of infertility affecting nearly 10-15% of married couples, India has nearly 27.5 million couples who seek treatment for their problem. Luteal phase support is essential and beneficial in assisted reproductive cycles to improve fertility outcomes. The importance of progesterone in early pregnancy has been known for many years; in the early 1970s studies demonstrated that the removal of the corpus luteum before the 7th week of pregnancy caused abortion, and this could be prevented by the administration of exogenous progesterone.[6,7] In 1999, the FDA also noted that use of exogenous progesterone for luteal phase support in IVF cycles had become routine and that the agency had itself recently approved a progesterone gel for use in infertile women under treatment with ART.[8]

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Table 1: Classification of progestogen hypersensitivity (also known as autoimmune progesterone dermatitis)

Classification	Triggering factors	Presentation
Endogenous		
Primary	Menses	Perimenstrual symptoms
	Pregnancy	Monthly symptoms after completion of non-IVF pregnancy
Exogenous		
Secondary	Supplemental progestogen*	Symptoms seen only during supplemental progestogen administration
Mixed$^{\Psi}$	Supplemental progestogen*	Administration of supplemental progestogen following which patient develops perimenstrual symptoms

IVF=*in vitro* fertilization. Adapted and Modified from Foer *et al*.[2] *Includes non-native progesterone and progestins. $^{\Psi}$Defined as an initial reaction due to exogenous exposure, with subsequent reactions to both exogenous and endogenous sources of progestogen

Materials and Methods

We undertook a comprehensive English literature search across multiple databases such as PubMed, SCOPUS, EMBASE, MEDLINE and Cochrane using keywords (alone and in combination) and they included 'progestogen hypersensitivity', 'autoimmune progesterone dermatitis', 'exogenous progesterone dermatitis', 'progesterone and IVF' and 'progesterone and infertility'.

We found 15 relevant articles after our search—3 original articles, 5 review articles and 5 case reports/letters/cameo and 2 clinical communications. Each article was meticulously analysed to obtain the following information: pathogenesis, clinical features, diagnosis, differentials and management. Additional data were obtained from the reference list of already selected articles. Articles not written in English were excluded as were clinical images and those describing other cases of cutaneous manifestations of IVF not associated with progesterone.

Role of progesterone in ART/IVF

Progestogen describes a group of steroid hormones that includes both progesterone and progestins. Progesterone is an endogenously synthesized hormone derived from cholesterol.[9] Progestins are synthetically derived by editing side chains on a different group of hormones, primarily 19-nortestosterone, 17 a-hydroxyprogesterone or acetoxyprogestin found in contraceptives and intrauterine devices (IUDs).[10] Hence, 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.

Women undergoing ART are the most appropriate candidates of luteal phase support (LPS). Cochrane 2015 recommends LPS in IVF and intracytoplasmic sperm injections (ICSI) cycles to improve implantation and pregnancy rates. It can be achieved by either progesterone or GnRH agonist/hCG to support corpus luteum to produce adequate progesterone.[11,12] It has been well-known since the 1980s and is today universally accepted that the luteal phase subsequent to IVF cycles in the absence of exogenous hormonal support is characterized by early luteolysis, followed by premature decline of oestrogen and progesterone levels. These abnormalities have a negative impact on endometrial receptivity and embryo implantation, with a significant reduction in success rates of IVF treatments.

European society of human reproduction and embryology (ESHRE) 2019 strongly recommends progesterone use for LPS in ART cycles.[13] It should be started between the day of oocyte retrieval to day 3 post-oocyte retrieval and to be continued for about 6-9 weeks or till the day of pregnancy test at least. Progesterone should be given till luteo-placental shift occurs.

Though luteal phase supplementation with hCG is associated with high-live birth rate or ongoing pregnancy rate but carries a greater risk for ovarian hyperstimulation syndrome (OHSS) compared with supplementation with progesterone,[14] administration of GnRH agonist by intranasal route has been found to be associated with significantly high ongoing pregnancy rates. Cochrane 2015 reported addition of GnRH agonist to progesterone further improve outcomes. Other commonly used medications in luteal phase to aid implantation process in ART are aspirin, heparin, prednisolone, and sildenafil.[15-18]

Progesterone is thus a very essential drug for luteal phase support protocols. Hence, hypersensitivity to progesterone is an important and difficult challenge to manage in these patients.

Epidemiology

Despite its description more than 50 years ago, epidemiology of PH is unknown but may be more common than realized. It affects women of childbearing age with the average age of onset in the third decade of life (mean age of 27.3 years (range 12-47) and 29.7 years (range 13-48) in 2 different studies).[2,19,20] Family history of PH is not thought to be a risk factor, but there is one case report of 3 sisters with PH.[21] A relationship between exogenous progestogen exposure and development of the disease has been documented in several studies.[2,20,22,23] Nguyen and Razzaque Ahmed found that 40 of the 89 (44.94%) cases they reviewed had known prior exposure to exogenous progestogen.[20]

Pathomechanism of PH

The exact underlying pathophysiology of PH is unclear and poorly understood, but given the heterogeneity of clinical manifestations and multiple mechanisms are likely.

This dermatosis, which is exclusively observed in women in child-bearing age, disappears completely with onset of menopause, an observation that highlights the importance of hormonal triggers.

a) One theory is that sensitization occurs with previous progesterone exposure (i.e. oral contraceptives, intrauterine devices containing progesterone, menarche, pregnancy) which results in formation of progestogen specific IgE antibodies (Type I Gell and Coomb's immediate hypersensitivity reaction) when subsequent exposure to a progestogen occurs, patients react because of cross-linking of these antibodies.[24]

   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.[2,22,25] However, there are multiple reports of patients who have never been exposed to exogenous progestogen who develop PH.[26-29]

   Positive immediate skin prick or intracutaneous testing to progesterone has been demonstrated in many patients with suspected PH.[30,31]

   Evidence of basophil and mast cell (MC), activation using functional assays also support an IgE-mediated immune response (Type I Gell and Coomb's immediate hypersensitivity reaction).[1,32,33]

b) Pathogenesis through mechanisms such as delayed hypersensitivity (Type IV Gell and Coomb's hypersensitivity reaction) through G protein-coupled receptor modulation of TH2 cells, through activation of progesterone membrane receptor α (PHR α) on CD8+ cells have also been suggested.[34]

c) An immune complex-mediated (Type III Gell and Coomb's hypersensitivity reaction) mechanism has also been proposed as one case report identified 17-hydroxyprogesterone-binding IgG immunoglobin in a patient's serum experiencing cyclical perineal rashes.[18,35]

d) A less accepted proposed mechanism for PH in patients with no prior exposure is progestogen sensitization developing after glucocorticoid exposure which shares similar chemical structure and hence may cause cross-sensitization. Evidence against this hypothesis is that numerous case studies of PH have reported successful treatment with glucocorticoids.[23,35-38]

Clinical features

Symptoms of PH vary widely and are elaborated in Table 2 and depicted in Figure 1. Dermatological findings are most common while in some patients, more than one type of dermatologic and nondermatological manifestations have been described.[39-42] Sood *et al*. in their prospective study in a cohort of 200 patients undergoing IVF in a tertiary care centre observed dermatological manifestations in 27% of the study group, with urticaria being the most common cutaneous finding seen in 13.5%, followed by acneiform eruptions (3%). Twenty-six (96.3%) patients who manifested with urticaria were on progesterone.[5] Similar findings were noted by Nguyen and Razzaque Ahmed in their study wherein 40 of the 89 (44.94%) cases they reviewed had known prior exposure to exogenous progestogen with 43 (48.31%) patients presenting with varying severity and extent of urticaria.[20]

Table 2: Clinical findings*

Dermatologic	Urticaria
	Angioedema
	Eczematous dermatitis
	Maculopapular rash
	Vesiculobullous/vesiculopustular lesions
	Petechiae/purpura
	Fixed drug eruption
	Stomatitis
	Erythema multiforme
	Pelvic region—vulvovaginal pruritus and labial swelling
Non-Dermatologic	Asthma
	Anaphylaxis

*Multiple simultaneous clinical findings occur in many patients

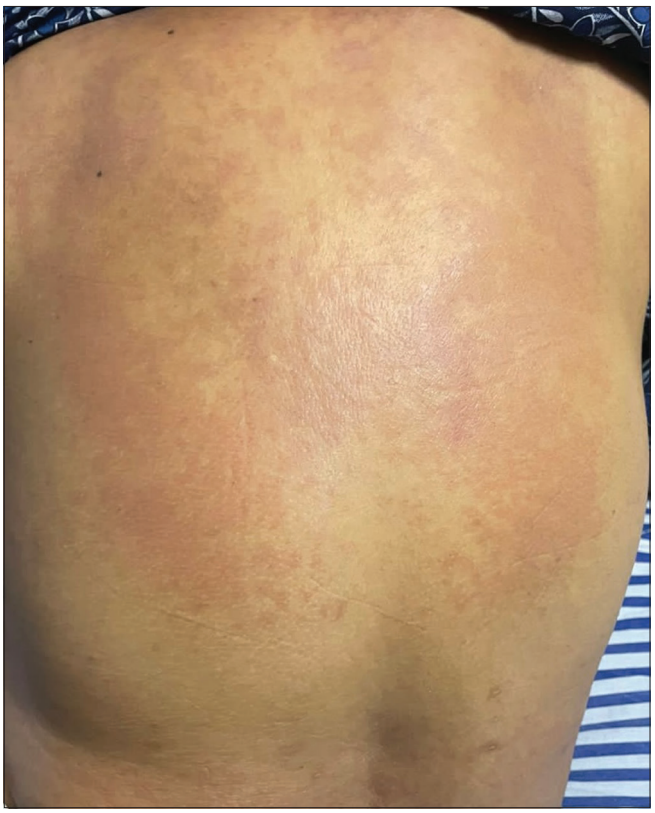

Figure 1: PH presenting as maculopapular rash

In endogenous PH, the timing of symptoms is most frequently associated with the endogenous progesterone surge of the luteal phase of the menstrual cycle, typically 3 to 10 days before menses as depicted in Figure 2. Therefore, the cyclical nature of PH is a diagnostic clue for clinicians

particularly for endogenous PH.[19] Symptoms triggered by exposure to exogenous progestins can limit the patient's ability to tolerate fertility treatment and achieve a desired pregnancy.[19,23] These do not necessarily correlate with the menstrual cycle and some women with PH have irregular menses. Patients with irregular menstrual cycles may have endogenous PH but may also be at an increased risk of PH due to exogenous progesterone exposure used to regularize the cycle.[19,28] Hence, diagnosis may be missed unless the clinician is aware of the polymorphic presentation of this condition and takes a detailed history.[28,43]

PH during pregnancy can be triggered by endogenous progesterone, additionally by the corpus luteum and/or placenta.[21,28,44,45] Among patients with pregnancy associated symptoms, PH can begin intrapartum and may or may not continue after childbirth or even begin postpartum.[46-48] Due to rise in systemic levels of progesterone in pregnancy, there have been reports of worsening of symptoms of PH.[19,23,37] Paradoxically, in patients with PH before pregnancy improvement in the intrapartum period has been proposed due to either auto desensitization as systemic levels of progesterone gradually rise during pregnancy or due to reduction in maternal immune response in pregnancy.[29,49,50]

The natural history of PH is also not well-defined, but there are reports of patients who have been followed long-term without remission of symptoms, whereas others go into remission at menopause.[31,41] There are no published reports of PH in postmenopausal women receiving progestins with hormone replacement therapy (HRT), but PH should be considered as a probable diagnosis in postmenopausal women on HRT if compatible clinical symptoms are present. The various differentials are as elaborated in Table 3.

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. Detailed history with relevance to drugs and symptoms during previous pregnancy is to be obtained. Relevant diagnostic modalities in clinical practice include progesterone skin testing and challenge.[9,25,51,52]

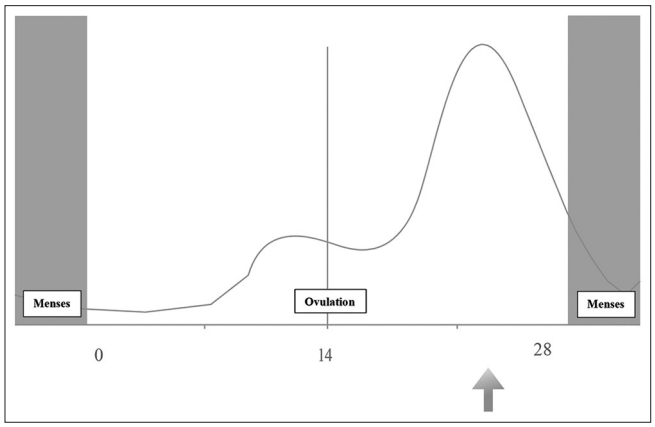

Figure 2: Endogenous PH and menstrual cycle. Symptoms of endogenous PH correlate with progesterone levels during the luteal phase of the menstrual cycle as depicted by the arrow

Skin tests: Progesterone skin prick and intracutaneous testing has been employed as a diagnostic test to confirm suspected PH. This test has been proposed to be helpful for identifying both immediate and delayed hypersensitivity in PH.[2,21,31,46,53] Autologous serum skin tests, with sera obtained during the follicular and luteal phases of the menstrual cycle, have also been proposed as a useful tool for diagnosis of PH.[52] Skin prick testing is conducted with progesterone (50 mg/mL) in serial dilutions. Wheal and flare are compared with diluent (either oil or ethanol) and positive histamine control.[2,25,54] Intracutaneous testing with synthetic progestins has been described; however, synthetic progestins often contain additives such as polyethylene glycol.[52,55] In a recent study of 24 patients with clinical history consistent with PH, only 50% of patients had positive progestogen skin testing.[2] 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 are unknown and cannot alone rule in or rule out PH.

Progesterone challenge has a limited use in the diagnosis of PH. Risks of challenge include symptom exacerbation.[1,9,19,56] Attempts at progesterone patch testing have not been shown to be a more useful diagnostic tool than existing modalities.[54] Several experimental tests used to diagnose PH include a direct leukocyte histamine release

Table 3: Differential diagnosis for progestogen hypersensitivity

Medications	Particularly nonsteroidal anti-inflammatory drugs commonly used in premenstrual period
Primary dermatologic pathology	Chronic idiopathic urticaria, atopic dermatitis, allergic contact dermatitis
Steroid hypersensitivity syndromes	
Catamenial anaphylaxis	It is believed to be due to an allergy to prostaglandins released at the time of menses resulting in multisystem allergic reactions.
Oestrogen hypersensitivity	Exogenous or endogenous oestrogen leads to premenstrual urticaria or delayed-type dermatitis with positive oestrogen skin test
Lactation anaphylaxis	Clinical correlation with breastfeeding or manual expression of breast milk

Adapted and modified from Foer D, Buchheit KM[8]

assay and a progesterone-specific immunoglobulin (Ig) E enzyme-linked immunosorbent assay used by Bernstein and colleagues.[41] An assay to detect interferon-gamma release also has been proposed.[57]

Management

Treatment for PH varies widely based on symptoms and long-term goals, but generally focuses on controlling specific symptoms or inducing anovulation if appropriate. Management of PH is as outlined in Figure 3. Interestingly, the specific progestogen trigger does not seem to matter in terms of responsiveness to medical management and treatment with desensitization.[1,31,48]

Medical management with antihistamines or corticosteroids (topical/oral) can be initiated for patients desiring symptom control.[29,42,58,59] Tolerance is variable and often limited by adverse side effects for long-term use. Three months has been proposed as a rational trial period for medication management, although this may be at the discretion of the patient and clinician. Patients not responding to symptom management may require suppression of ovulation or desensitization.

Suppression of ovulation with oral contraceptive pills (OCPs) has been shown to effectively control symptoms in several patients. However, some patients cannot tolerate the low-dose progestin in OCPs and instead require treatments with other medications that suppress ovulation, like gonadotropin-releasing hormone (GnRH) agonists, alkylated androgens and tamoxifen.[44,49,60-63]

Symptoms of hypoestrogenemia with GnRH agonists and tamoxifen, and androgen-induced side effects, with the 17-a-alkylated steroids severely limit their use. Huang *et al*. were the first to report their experience with effective treatment of progesterone-induced dermatitis with etonogestrel Implants (68 mg) skin embedding treatment while mifepristone tablets (25 mg) therapy for two months was considered not so effective.[34] Oophorectomy has been employed as a definitive treatment for patients with severe PH of endogenous or mixed aetiology, that cannot otherwise be managed medically although should be considered only in rare refractory cases or based on patient preference and not in women who still wish to conceive.[1,26,27,64,65]

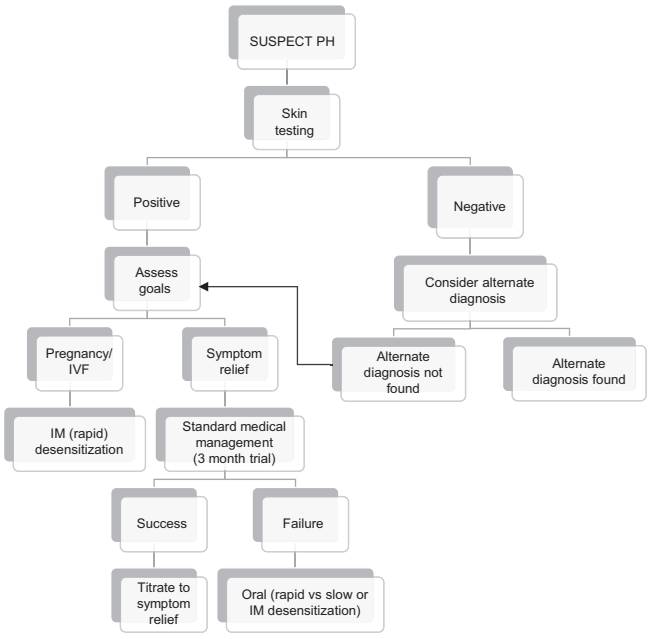

Figure 3: Management tool for evaluation and treatment of PH adapted and modified from Foer *et al*.[2]

Recently omalizumab, an anti-IgE monoclonal antibody has also been used successfully to treat PH patients experiencing cyclic urticaria with angioedema and other systemic anaphylactic symptoms.[66] 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.[67]

Progesterone desensitization: It 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.

Another important indication is for patients undergoing fertility treatment/IVF requiring supraphysiological high-dose progesterone, as symptom management is not an option, and omission of progesterone which is crucial during LPS is not feasible. 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 and enable successful outcomes.

There are now many reported cases of successful treatment outcomes with progestogen desensitization.[2,4,20,22,67] The first evidence of successful P desensitization in patients requiring IVF culminating in successful pregnancies was by Prieto-Garcia *et al.* in 2011.[22] They reported six cases of APD, three related to IVF and treated with desensitization, resulting in viable pregnancies. Because patients require IVF and there is no alternative to progesterone, desensitization was needed to achieve viable pregnancies. Skin tests were performed with progesterone for IVF which were positive in all patients and negative in 10 controls, and rapid 8- and 10-step progesterone desensitization protocols were performed, with increasing doses administered every 20 minutes via intravaginal suppositories. A rapid oral desensitization protocol was performed in one patient who required an oral contraceptive for uterine bleeding. The desensitization protocols are detailed in Table 4.

The exact mechanism by which desensitization to progesterone induces tolerance is unknown but may be secondary to IgE-dependent tolerance observed with desensitization to other drugs.[68-70]

In patients with dermatitis-type symptoms, slow oral desensitization protocols have been used successfully. One such protocol is to use a combined OCP containing oestrogen and progestin. 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. After desensitization, patients are continuously cycled on the OCP, so that there is no cessation of progesterone exposure leading to resensitization.

However, in the case of patients undergoing IVF treatment for infertility, a rapid IM protocol has previously been used successfully. Although intramuscular (IM) and vaginal protocols appear to have equal efficacy, IM has been recommended as the easiest modality for rapid desensitization.[1,31,71] 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.[2,19]

The timing of the desensitization protocol relative to embryo transfer is determined in collaboration with a reproductive endocrinologist. The various treatment options are summarized in Table 5.

Table 4: Desensitization protocols

A) Slow oral desensitization protocol for a progestin			
Day	**Dose (based on progestin composition)**	**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

B) Rapid IM protocol	
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. Adapted and Modified from Foer *et al*.[2]

Successful outcomes with progesterone desensitization in cases of exogenous PH and IVF

Prieto-Garcia *et al*. in 2011 published the first evidence of successful progesterone desensitization in four patients out of six with three patients requiring IVF culminating in successful pregnancies.[22] They reported six cases of APD, three related to IVF and treated with desensitization, resulting in viable pregnancies. Among the three patients who had symptoms related to IVF, one patient had an exacerbation of her previous APD during IVF while the other 2 had symptoms for the first time after exogenous P administered for IVF. These latter patients did not have cyclic manifestations related to menses, which may be representative of hypersensitivity to exogenous but not endogenous P. Higher than physiologic levels or the presence of chemically slightly different P may be necessary to trigger clinical manifestations of MC activation in these cases.

In 2016, Foer *et al*. reported the largest case series of patients with PH with successful treatment outcomes.[2] Twenty-four cases of PH were evaluated retrospectively.

Table 5: Treatment options in progestogen hypersensitivity

Treatment category	Class of drugs	Possible outcomes/ complications
Symptomatic relief	Oral antihistamines	Incomplete efficacy
	Topical glucocorticoids	Incomplete efficacy
	Systemic glucocorticoids	Incomplete efficacy, long-term side effects
Ovulation suppression		
Medical	Combined oral contraceptive pills	Possible hypersensitivity reaction to low-dose progesterone
	GnRH agonists (i.e. leuprolide)	Oestrogen withdrawal symptoms
	Selective oestrogen-receptor modulators (i.e. tamoxifen)	Oestrogen withdrawal symptoms
	17-a-Alkylated steroids (i.e. stanozolol, danazol)	Hirsutism, mood changes, LFT abnormalities
Surgical	Oophorectomy	Premature menopause, permanent loss of fertility
Desensitization	Rapid desensitization to oral, IM, or intravaginal progestogens	Resource intensive, risk of hypersensitivity reactions during desensitization
	Slow desensitization to oral progestins	Risk of hypersensitivity reactions during desensitization

GnRH=Gonadotropin-releasing hormone, IM=Intramuscular, LFT=Liver function test. Adapted and Modified from Buchheit KM, Bernstein JA[18]

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. It was successfully demonstrated that progestogen desensitization is successful in multiple patients and can result in symptom control and fertility.

A study conducted in South Korea retrospectively reviewed data from patients presenting with dermatitis induced by exogenous progesterone between 2011 and 2016.[4] Out of nine patients who had exogenous PH, six patients were treated with progesterone for threatened abortion, and three for ARTs. Skin tests were performed in four patients; all were positive. All patients were treated with antihistamines, and six patients were treated with systemic corticosteroids. Two patients were treated successfully by progesterone desensitization. While one suffered an adverse reaction after administration of progesterone for a threatened abortion, and subsequently underwent desensitization therapy because administration of progesterone was required as a sterilization procedure. Two patients tolerated the desensitization procedure with no hypersensitivity reaction. No patient experienced cyclic skin eruptions following exogenous progesterone–induced dermatitis, but two developed chronic urticaria.

Conclusion

Changing sociodemographic patterns with an increase in the age of childbirth have affected fertility rates worldwide and with advancing reproductive medicine, assisted reproductive techniques (ART) are becoming common. *In vitro* fertilization treatments are being used with greater frequency, and probably PH will be observed more often. The massive exposure to supraphysiologic doses of progesterone used for IVF may increase the likelihood of sensitization. Progesterone desensitization expands the treatment options for women with APD beyond simply suppressing ovulation and represents the only treatment option currently available that preserves the patient's fertility and resulting in successful pregnancies.

As use of progesterone increases, an understanding of the clinical features of exogenous PH becomes ever-more important. Therefore, clinicians should be cognizant of PH, its clinical manifestations and available treatments.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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