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Progesterone Dermatitis (Progestogen Hypersensitivity) Presenting as a Polymorphic Drug Eruption After Oral Norethisterone: A Case Report

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Abstract

Progestogen hypersensitivity (PH) describes hypersensitivity reactions to endogenous progesterone, classically termed autoimmune progesterone dermatitis, or to exogenous progestogens. Non-cyclical presentations can be difficult to distinguish from other dermatoses. We describe a case of a 46-year-old woman who developed a widespread pruritic rash 52 days after starting oral norethisterone for heavy menstrual bleeding. The rash began on her arms and progressed to involve the trunk and legs, with papules, pustules, confluent erythema, and crusting. Purpuric, targetoid lesions later developed on her lower legs, followed by pompholyx-like vesicles on her palms and a periorbital eczematous rash.

Her eosinophil count was 1.2×10^9/L (normal range: 0.02-0.50x10^9/L) and C-reactive protein 16 mg/L (normal range: <5 mg/L). She was afebrile, with no mucosal involvement and no evidence of hepatic or renal dysfunction at presentation. Herpes simplex and varicella-zoster PCR were negative. Skin biopsy showed acanthosis, parakeratosis, and spongiosis, with a dermal infiltrate of lymphocytes and eosinophils. The clinical differentials included a drug eruption, pustular folliculitis, atypical pityriasis rubra pilaris, and erythema multiforme. Norethisterone was stopped, and she was treated with potent topical corticosteroids and a six-week tapering course of oral prednisolone, starting at 30 mg daily. Her skin was largely clear about nine weeks after norethisterone was stopped, with no relapse to date. Discussion at the clinicopathological meeting concluded that this was a delayed-type hypersensitivity reaction to norethisterone, consistent with exogenous PH. She declined a progesterone challenge and was advised to avoid progestogen-containing hormone therapy. This case describes a polymorphic, non-cyclical presentation of PH caused by an oral synthetic progestogen. It may complicate future management of menopausal symptoms, as women with an intact uterus usually require a progestogen alongside estrogen therapy to protect the endometrium.

Categories: Obstetrics/Gynecology, Allergy/Immunology, Dermatology
Keywords: autoimmune progesterone dermatitis, cutaneous drug eruption, delayed-type hypersensitivity, eczematous rash, menstrual bleeding, norethisterone, progestogen hypersensitivity

Introduction

Progestogen hypersensitivity (PH) is a rare, heterogeneous group of reactions to progesterone or synthetic progestogens [1-4]. It was historically called autoimmune progesterone dermatitis (APD), a cyclical eruption flaring in the luteal phase as endogenous progesterone peaks [5,6]. The broader term PH was proposed after recognizing that patients first react after an exposure to exogenous progestogens, such as oral contraceptives, in vitro fertilization (IVF) luteal support, and progestogen-releasing devices [1,7]. Exogenous exposure is a common trigger. Initial symptoms followed an exogenous progestogen in 58% of women with PH in one review, and in nine of 14 in a recent case series [4,8].

Cutaneous manifestations of PH include urticaria, angioedema, eczema, erythema multiforme-like, bullous and fixed drug eruption-like lesions, as well as anaphylaxis [2,4,6,9]. Histology is non-specific, and the diagnosis requires a clinical history, a temporal relationship to progesterone exposure and, where possible, a progesterone challenge [4,9]. Ovulation suppression and, in refractory cases, bilateral salpingo-oophorectomy have the most favorable reported outcomes for treating cyclical progesterone dermatitis [6,7].

Norethisterone (norethindrone) is a 19-nortestosterone-derived progestogen [4]. Cyclical oral progestogens are a recommended treatment option for menstrual bleeding in UK national guidance [10]. Cutaneous hypersensitivity to oral norethisterone is rarely described. We report a widespread, polymorphic eruption with targetoid and eczematous features after oral norethisterone, which was initially thought to be pustular folliculitis or pityriasis rubra pilaris. Further dermatology review attributed it to a delayed-type hypersensitivity reaction to the progestogen.

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Case Presentation

A 46-year-old woman presented to the emergency department following a five-day history of a pruritic, mildly painful rash. It began on both arms and spread to the trunk and the legs. Oral norethisterone 350 µg (Noriday) once daily had been started 52 days prior to onset for heavy menstrual bleeding. Her other regular medications included longstanding ramipril, amlodipine, omeprazole, amitriptyline, indapamide, bisoprolol, and aspirin. She also took over-the-counter vitamin D for several years. There had been no recent dose changes, no new over-the-counter herbal or topical products, and no preceding illness or recent travel. Her medical background included hypertension, surgically closed atrial septal defect, iron deficiency anemia, and a probable hemiplegic migraine under neurology review. Regarding her skin, there was no prior inflammatory skin disease of note, though she reported mild hay fever and occasional dry skin managed with emollients. She reported a childhood rash with co-trimoxazole. In the emergency department, she had a widespread, blanching papulopustular rash with excoriations noted. Initial blood tests showed a normal white cell count, eosinophil count, and liver and renal function, with a C-reactive protein (CRP) of 14 mg/L (normal range: <5 mg/L). Remote dermatology advice suggested a possible pustular folliculitis or pityriasis rubra pilaris. She was treated with topical clobetasone-oxytetracycline-nystatin cream, fexofenadine, and oral flucloxacillin, which was later switched to clarithromycin.

On day 11 after onset, the eruption became markedly more florid. It had now developed into confluent erythema on the upper arms with yellow crusting, papular and targetoid lesions on the forearms and dorsal hands, scattered pustules and papules across the abdomen, back, and buttocks (Figure *1*). There was a confluent erythema noted on the thighs, with scattered vesicles and targetoid purpuric lesions on the lower legs (Figure *2*). Dermatology considered this polymorphic appearance in keeping with a drug eruption. The eosinophil count had risen to $1.2x10^9$/L (normal range: $0.02\text{-}0.50x10^9$/L) and CRP to 16 mg/L. Norethisterone was identified as the only new drug prior to onset and was stopped along with the antibiotics that had been started following development of rash. Skin swabs were then taken and came back negative for herpes simplex virus and varicella-zoster on PCR.



FIGURE 1: Clinical appearance of eruption of arm.

Lateral view of the right arm, showing confluent erythema with papules and excoriations.

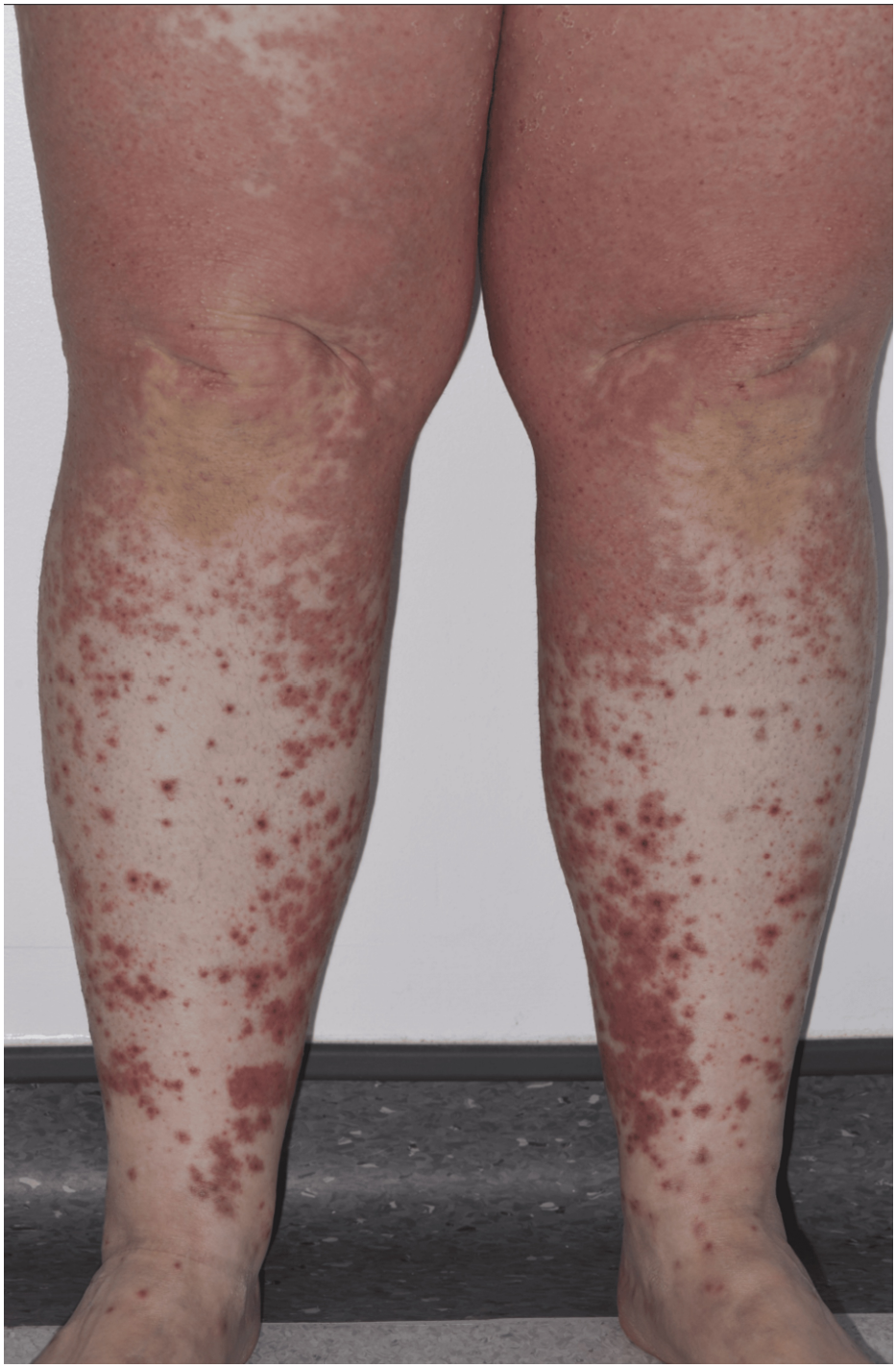


FIGURE 2: Clinical appearance of eruption on the lower legs.

Lower legs showing purpuric, targetoid papules coalescing into confluent erythema.

At the dermatology review on day 14, she reported periorbital itching. Examination revealed a predominantly papular eruption coalescing on the arms and legs, superficial desquamation of the trunk, and eczematous patches around the eyes and cheeks (Figures *3*-*5*). There was crusting on the dorsal wrists of both hands (Figure *6*). There was no mucosal involvement or lymphadenopathy, and she was systemically well. A 6-mm punch biopsy was taken from the left upper arm. Treatment was started with betamethasone valerate 0.1% ointment to the body, clobetasone butyrate to the face, 1% hydrocortisone periorbitally, fusidic acid-betamethasone to the crusted areas, and Dermol 500 as a soap substitute.



FIGURE 3: Papular eruption on day 14.

Left upper arm showing a predominantly papular eruption coalescing into confluent erythema. The dressing marks the site of the 6-mm punch biopsy.

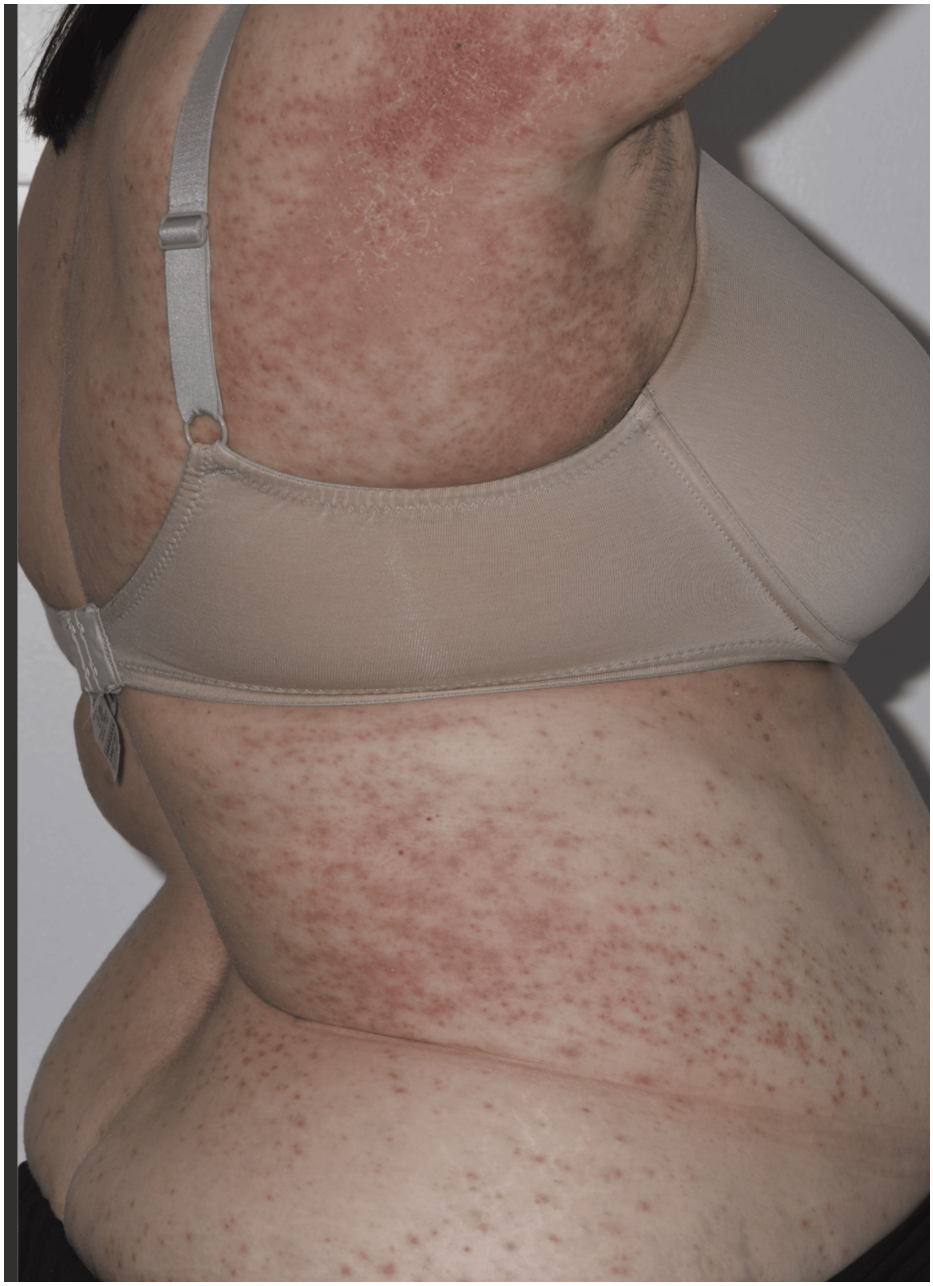


FIGURE 4: Widespread papular eruption involving the trunk.

Lateral view of the trunk showing a widespread papular eruption with superficial desquamation on the upper back.



FIGURE 5: Eczematous patches on cheek.

Eczematous patches with fine papules on the cheek. The periorbital area has been obscured for patient anonymity.



FIGURE 6: Dorsal wrist and hand.

Erythematous plaques with crusting over the dorsal wrist and scattered papules across the dorsum of the hand.

Histology showed acanthosis, orthokeratosis and parakeratosis, mild spongiosis, and a dermal infiltrate of lymphocytes and eosinophils. There was focal vacuolar degeneration of the basal layer without vesiculation (Figure 7). The features were not typical of pityriasis rubra pilaris and were consistent with an eczematous process or a drug reaction.

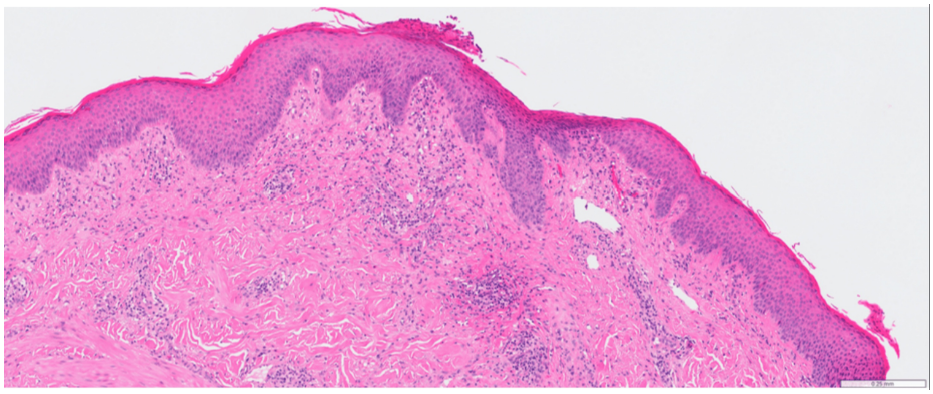


FIGURE 7: Skin biopsy, upper left arm (hematoxylin and eosin staining).

Mild acanthosis with a mound of parakeratosis, spongiosis, and exocytosis of a few small lymphocytes, and a focal mild vacuolar degeneration of the basal layer.

On day 19, she developed new vesicles on the palms and forehead and patchy erythema on the chest. On review of clinical photography, these resembled pompholyx hand eczema. Clobetasol propionate 0.05% ointment was prescribed for the hands. As the vesicles had persisted, oral prednisolone was commenced on day 21 with an initial 30 mg for seven days and then a 5-mg tapering schedule over the next six weeks. By day 28, the eruption was fading. Prednisolone was subsequently stopped on day 63.

This case was then discussed at the dermatological clinicopathological meeting on day 56. The consensus was a delayed-type hypersensitivity reaction to norethisterone with polymorphic features, consistent with exogenous PH. At review on day 74, around nine weeks after stopping norethisterone, the skin was largely clear. Mild eczematous papules remained on the inner arms and thighs, which responded to emollients and intermittent topical betamethasone. Blood tests showed a mildly raised alanine aminotransferase (ALT) (57 U/L; normal range: <33 U/L) and alkaline phosphatase (ALP) (116 U/L; normal range: 30-130 U/L), normal bilirubin, and normal C3 (1.44 g/L; normal range: 0.75-1.65 g/L) and C4 (0.33 g/L; normal range: 0.14-0.54 g/L). Autoantibodies, including anti-gastric parietal cell, anti-mitochondrial, anti-smooth muscle, and antinuclear antibody (ANA), were negative. The patient was amenorrheic since stopping norethisterone and had no cyclical skin symptoms. She declined progesterone challenge due to being amenorrheic and was advised to avoid progestogen-containing hormone therapy. The timeline is summarized in Table *1*.

Day	Event
-52	Oral norethisterone 350 µg (Noriday) started for heavy menstrual bleeding
0	Pruritic rash appears
5	ED: papules and pustules, CRP 14 mg/L, eosinophils normal
7-11	Flucloxacillin oral then clarithromycin
11	Florid polymorphic eruption with targetoid leg lesions, eosinophils: $1.2x10^9$/L, CRP: 16 mg/L, HSV and VZV PCR negative
14	Dermatology review, punch biopsy, betamethasone started with topical Fucidin
19	Pompholyx-like palmar and forehead vesicles, topical clobetasol started
21	Oral prednisolone 30 mg started, tapered over six weeks
56	CPC meeting; determined it was a delayed hypersensitivity to norethisterone
63	Prednisolone stopped
74	Skin largely clear, mild residual eczematous papules; progesterone challenge declined by patient

TABLE 1: Timeline of clinical course (day 0=rash onset).

HSV: herpes simplex virus; VZV: varicella-zoster virus; CPC: clinicopathological conference

Discussion

We believe the drug eruption was most likely due to suspected exogenous progestogen hypersensitivity (PH) following oral norethisterone use, although the diagnosis cannot be confirmed. Norethisterone was the only new medication introduced prior to the onset of symptoms, with a latency of 52 days, suggesting a delayed T-cell-mediated reaction. The eruption resolved after discontinuation of norethisterone, and histology supported this further, showing spongiotic dermatitis with eosinophils consistent with a drug-related eruption. However, these histological features are not specific to PH, and in the absence of a progestogen challenge, this association remains probable rather than established.

Unlike classical autoimmune progesterone dermatitis (APD), which typically presents with cyclical eruptions during the luteal phase, our patient had no prior history of symptoms during her menstrual years [1,5]. The eruption only developed following synthetic progestogen exposure. Current diagnostic criteria for PH recognize reactions associated with exogenous progestogen exposure, even in the absence of cyclical symptoms [4]. This presentation is consistent with the exogenous form of PH previously described by Foer et al. [1,9]. Although these features can be compatible with a delayed-type drug reaction, we have framed this within the PH spectrum due to this being the preceding drug and having implications for future progestogen exposure and hormonal therapy.

Our differential diagnosis changed as the eruption progressed. Drug reaction with eosinophilia and systemic symptoms (DRESS) was considered in view of delayed onset, eosinophilia, and widespread rash. However, she was afebrile with no lymphadenopathy and no evidence of end-organ involvement at presentation. Retrospective Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring gave a total score of 2, but the mild ALT rise at follow-up did not meet criteria for hepatic involvement and remained stable at five months (59 U/L), suggesting an unrelated cause [11]. Acute generalized exanthematous pustulosis was also considered unlikely, given the scattered appearance rather than confluent pustules, absence of fever or neutrophilia, and histological findings.

Identifying the causative drug was complicated by two aspects of the clinical course. From day seven, she received flucloxacillin, then clarithromycin. However, these were started after the onset of the eruption. New pompholyx-like vesicles additionally appeared one week after the norethisterone was discontinued. However, delayed drug eruptions can continue to evolve following drug withdrawal, and pompholyx-type reactions are a recognized drug reaction pattern [12].

The underlying mechanism of PH is not fully understood, although type I, III, and IV hypersensitivity reactions have been proposed. A multiple-hit model has also been suggested, where progestogen exposure alone may not be sufficient to trigger symptoms [2-4]. Clinical presentations vary considerably, ranging from urticaria and anaphylaxis to dermatitis and fixed drug eruptions [4,6,9]. In our patient, the polymorphic eruption, delayed onset, and histological findings were suggestive of a T-cell-mediated reaction. Dermatitis was reported in four of 14 patients in a recent case series, although most descriptions of eczematous PH involved cyclical flares [8,13]. Reports of non-cyclical polymorphic eruptions following oral synthetic progestogen exposure remain limited. Diagnosis can be challenging, as progesterone skin testing has limited sensitivity and specificity, and a negative result does not rule out PH. A progestogen challenge may therefore be considered to help confirm the diagnosis, although this is not always appropriate or safe [4,9].

The diagnosis also raises questions about future menopausal hormone therapy. Our patient is perimenopausal and has remained amenorrheic since stopping norethisterone. If she requires estrogen therapy in the future, progestogen would ordinarily be prescribed to provide endometrial protection. This presents a potential management difficulty given her hypersensitivity to norethisterone. Cross-reactivity is unpredictable; patients with exogenous PH may react to one progestogen yet tolerate others, and PH has not been reported in postmenopausal women taking progestogens as hormone therapy [4]. Instead of complete avoidance of progestogens, individualized assessment through allergy services would be appropriate. The levonorgestrel-releasing intrauterine system (IUS) gives low systemic progestogen levels; however, urticarial reactions have been reported [14,15]. Other options include a tissue-selective estrogen complex or conjugated estrogens with bazedoxifene, which protects the endometrium without a progestogen and may be an option where available, ideally requiring gynecology input prior to this [16]. For heavy menstrual bleeding, non-hormonal options also include tranexamic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), and endometrial ablation. This report has limitations. The diagnosis rests on clinical and temporal grounds, as the patient did not want a progestogen challenge or skin testing. The histological findings are not specific to PH, and improvement coincided with both norethisterone withdrawal and steroid administration, which confounds causality.

Conclusions

Exogenous progestogen hypersensitivity can present as a non-cyclical, polymorphic drug eruption with targetoid and eczematous features weeks after starting oral norethisterone. Eruptions like these can easily be misdiagnosed as folliculitis, pityriasis rubra pilaris, or erythema multiforme. A history of recent progestogen use is therefore important in women presenting with a new widespread rash, even in the absence of a cyclical pattern. The diagnosis also has implications for future treatment, particularly when

considering contraception, management of heavy menstrual bleeding, and menopausal hormone therapy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ishika Singh

Acquisition, analysis, or interpretation of data: Ishika Singh, Maneesha Vatve

Drafting of the manuscript: Ishika Singh

Critical review of the manuscript for important intellectual content: Ishika Singh, Maneesha Vatve

Supervision: Maneesha Vatve

Disclosures

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