

Clinical Commentary Review

Hormonal Effects on Urticaria and Angioedema Conditions

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Women appear to be more frequently affected with urticaria and angioedema. Sex hormones are believed to have an important mechanistic role in regulating pathways involved in these conditions. This effect is likely nonspecific for chronic spontaneous urticaria (CSU) or many forms of angioedema (AE), because many other chronic diseases such as asthma are also affected by sex hormones. The role of sex hormones has been better elucidated for hereditary AE, because they have been shown to have multiple effects including upregulation of FXII, an important activator of the kallikrein pathway. However, their role in the underlying pathogenesis for CSU is less clear. Autoimmunity is clearly linked to CSU, which is more common in women. This suggests that sex hormones could act as adjuvants in activating or upregulating autoimmune pathways. The purpose of this review is to discuss in detail the role of sex hormones in CSU and AE and how a better understanding of the impact hormones has on these conditions might lead to new treatment advancements with better clinical outcomes. © 2021

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INTRODUCTION

Chronic spontaneous urticaria (CSU), defined as wheals and/or angioedema (AE) with or without an inducible component (chronic inducible urticaria [CIndU]), is not a trivial disease and can be challenging to manage and treat. Current evidence-based guidelines and validated patient-reported outcome measures are available to help clinicians assess the severity of urticaria and control and initiate appropriate therapy to achieve the ultimate goal of management, which is a lack of hives and swelling.¹ However, only approximately 40% to 50% of patients respond to step 2 therapy, which is up to four times the US Food and Drug Administration—recommended dose of H1-antagonists.² These refractory patients may require further investigation to determine whether they are experiencing a specific type of urticaria, such as autoimmune urticaria, urticaria vasculitis, neutrophilic urticaria, or cyclic hypersensitivity (ie, progesterin hypersensitivity), which could be obfuscating treatment. Furthermore, isolated AE may be histaminergic (ie, responsive to H1-antihistamines or step 3 or 4 treatment guidelines) or non-histaminergic, which may infer that other mediators such as bradykinin (BK) are involved.³ In both instances, women appear to be more frequently affected with these conditions for unclear reasons, but sex hormones are believed to have an important role. The purpose of this review is to discuss in detail the role of sex hormones in histaminergic CSU and AE and BK mediated hereditary AE (HAE) and how a better understanding of the impact that hormones have on these conditions might lead to new treatment advancements with better clinical outcomes.

EPIDEMIOLOGY OF CSU AND AE: ARE HORMONES RESPONSIBLE FOR THE GREATER NUMBER OF WOMEN WITH THESE DISORDERS?

Prevalence

A recent systematic review with meta-analysis⁴ estimates that CSU is a relatively common disease with an overall point prevalence across all age groups of 0.7% and an adjusted lifetime prevalence of 1.4%. However, there are substantial differences among regions of the world. In North America, the prevalence is only 0.1%,^{5,6} in Europe it is 0.5%,⁷⁻⁹ and in Asia and Latin America it is 1.4%¹⁰⁻¹² and 1.5%, respectively.¹³ Like other immune-mediated allergic and autoimmune diseases,¹⁴ the prevalence of CSU is increasing.¹⁵ It was traditionally accepted

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that the prevalence in children was lower than in adults,¹⁶ but new data demonstrate that the summary point prevalence estimate for children (1.43%) is actually slightly higher than for adults (0.86%).⁴ Sex-specific analysis in children aged less than 15 years shows no sex-specific differences, with a point prevalence of 1.0% for girls and 1.1% for boys. In contrast, the prevalence of asthma and allergic rhinitis¹⁷ is higher in boys¹⁴ and during adolescence to young adulthood there is a switch toward female predominance. The reason for this transition is unclear, but sex hormones are believed to have an important role.¹⁴ It is hypothesized that the higher prevalence of chronic urticaria (CU) in adult women (1.3%) compared with men (0.8%) is hormonally influenced.⁴ A recently published study from South Korea found a predominance of women for new-onset CU between ages 20 and 64 years¹⁸ and not in childhood¹⁹ or the elderly population,²⁰ which supports the hypothesis of a hormonal role. However, this sex-dependent difference is statistically significant only in Northern America and Europe and not in Asia,⁴ because several previous Asian studies failed to demonstrate a female predominance that affects the established male to female ratios of 1:2 or higher when they are included in this global demographic analysis.²¹⁻²⁴

Data from a large prospective, cross-sectional, questionnaire-based epidemiologic investigation in China also revealed a slight predominance of women (58.4%) with CIndU.²⁵ More females were affected with cold contact urticaria (65.9%) and dermographism (57.8%) whereas more males experienced cholinergic urticaria (84.4%).²⁵ However, most studies did not distinguish between CSU and CIndU, so future studies are needed to clarify the impact of hormones on these urticaria subtypes.

In general, CSU is more prevalent in women from after puberty until menopause, but this prevalence is not as apparent before puberty or after menopause, likely owing to hormonal influences.

Role of sex hormones influencing susceptibility

Sex hormones are thought to be responsible for sex differential susceptibility and the severity of some immune-mediated diseases including CU.²⁶ However, contrary to bradykinin-induced AE, in which the role of sex hormones is clearly demonstrated, their impact on the clinical course and severity of urticaria is modest. Bork et al²⁷ reported that of 103 women with histaminergic AE, none experienced new or worsened AE associated with the use of oral contraceptives (OCPs) and hormone replacement therapy (HRT).²⁵ A French cross-sectional study composed of interviews from 200 women consulting for CSU at nine centers throughout France found that hormonal contraception was an aggravating factor in 10% of those women.²⁸ Pregnancy may worsen or improve CSU and AE, according to anecdotal case reports and case series.^{28,29} However, in a report by Zhong et al,²⁵ there was no sex difference in CSU severity, and the association between wheals and menstruation was reported by only 4.8% of 1113 female participants with CSU. In contrast, Kasperska-Zajac and Zamlynski³⁰ suggested a causative role of sex hormones in a woman with an irregular menstrual cycle and severe CSU who improved after starting OCPs. An increasing number of childbearing-age women have also been affected by progesterone hypersensitivity, which further supports an important role of sex hormones in CSU.³¹

Role of autoimmunity

Perhaps the best way to understand the role of sex hormones in CSU is in the context of autoimmunity. The immune response is generally stronger in women, which makes them less susceptible to infectious diseases, but paradoxically, approximately 80% of people with autoimmune disease are women.³² Autoimmune diseases affect 5% to 10% of the western population and average age of onset is 40 to 50 years.³³ Many autoimmune diseases, especially systemic lupus erythematosus, Sjögren syndrome, Graves' disease, and Hashimoto thyroiditis have a strong female sex bias,³⁴ because they are seven to 10 times more common in women than men. Confino-Cohen et al³⁵ reported in a large study of 12,778 military servicemen and women that hypothyroidism was present in 9.8% with CSU, and more so in women compared with a prevalence of 0.6% in a matched control group. In general, female sex has a much higher risk for autoimmunity, which tends to increase during puberty and declines later in life owing to possible reduced hormonal effects.³⁶ Studies investigating the origins of sex differences in autoimmune disease revealed that sex hormones are involved through receptors that are widely expressed on a number of immune cells, and estrogen and androgen response elements are found in the promoter regions of several innate immunity genes.³⁶ Progesterone (PR), which is a key promoter of immune tolerance during pregnancy, is generally immunosuppressive.³⁶ It is present at high levels during the luteal phase of the menstrual cycle and in pregnancy. Estrogen levels are higher in pregnancy, lower in menopause, and variable across the menstrual cycle. However, its effect on the immune system is more complicated. At high concentrations, estrogens promote a T_H2 response, but in low concentrations a T_H1 response with immunostimulatory effects.³⁷ Androgens predominantly suppress the immune response.³⁸

Genetic influences

Genes also are important regulators of this network. The presence of two X chromosomes in the female contribute to the sex bias of autoimmunity. Although one of the X chromosomes is inactivated early in life, this process is imperfect because approximately 15% of genes escape the X chromosome inactivation. This explains why X chromosomes have many genes with established roles in autoimmunity.³⁹ In addition, the X chromosome contains 10% of the approximately 800 microRNAs in the human genome, whereas the Y chromosome contains only two microRNAs. MicroRNAs have a role in sex differences in immune responses and their expression can be under sex hormone control.⁴⁰

Epigenetics also has a role, because sex bias is prominent in DNA methylation and is influenced by the X and Y chromosomes, which affect chromatin accessibility by immune genes.⁴¹ The gut microbiota is in constant interplay with the immune system and both express sexual dimorphisms. There is increasing evidence that the gut microbiota is involved in sex-biased autoimmunity, with an overall trend toward enhanced innate immunity and attenuated adaptive immunity in the male relative to the female gut.⁴²

Thus, the higher prevalence of CSU among women is likely associated with sex hormones; this involves a complex network of genetic, microbial, and environmental factors.³²

PATHOGENIC ROLE OF FEMALE SEX HORMONES ON MAST CELLS AND THE KALLIKREIN-KININ SYSTEM

Mast cells and female sex hormones

Mast cells (MCs) are a common cellular component of connective and mucosal tissues; they contain a wide range of biologically active molecules that, when released, exert a spectrum of physiologic effects depending on the organ(s) affected. In addition to activating high-affinity IgE receptors, many MC receptors can activate and/or modulate MCs, including estradiol (ER) and PR receptors. Different authors demonstrated the expression of ER and PR receptors in mouse, rat, and human MCs.⁴³⁻⁴⁵ Estradiol receptor α -mRNA expression has been shown in human and mouse MCs⁴⁶ and 17 β -estradiol (E2) specific for ER α has been shown to stimulate MC degranulation *in vitro* and *in vivo*, resulting in the rapid release of preformed and newly formed mediators; moreover, they can be inhibited by the specific ER antagonist tamoxifen.⁴⁴ In contrast, testosterone had no effect on MC degranulation, which suggests that MCs do not express testosterone receptors.⁴⁷ Unsurprisingly, MCs from female rats are more susceptible to the effects of sex hormones compared with male rats. Of note, E2 exposure and antagonistic blockade can regulate MC histamine release in a dose- and sex-dependent manner.⁴⁸ Furthermore, they can differentially modulate MC degranulation, depending on whether they are used alone or as pretreatment followed by stimulation with neuropeptide substance P or by IgE receptor activation. Progesterone can inhibit MC secretion whereas E2 augments MC activation. The lowest PR concentration capable of some degree of inhibition is still higher than the mean serum PR found in the third trimester of pregnancy and mean postovulatory levels.⁴⁹

Mast cells are present in the uterus, ovaries, and mammary glands in many species including humans.⁵⁰⁻⁵² Their density fluctuates during the estrous cycle. Ovariectomized mice compared with non-ovariectomized control mice have fewer uterine and mammary MCs, and hormonal replacement has been shown to restore MC numbers. Estradiol-induced ovarian MC degranulation may be an important factor for ovulation.⁵³ In animal studies, there is an increased number of MCs in endometriomas; their activation correlates with serum E2 levels and the release of TNF and nerve growth factor involved in endometriotic pain.⁵⁴ Mast cells and their mediators are believed to be involved in implantation, pregnancy, and delivery.⁵⁵ Investigations into placental samples obtained after abortions revealed that the number of placental MC chymase-positive subtype cells increased. However, the positive or negative effect of MCs in pregnancy requires further elucidation.

The presence of estrogen receptors on bladder MCs was demonstrated by immunohistochemical analysis in patients with chronic interstitial cystitis.⁵⁶ In a rat model, bladder MC activation was augmented by ER.⁵⁷ Upper-airway MCs also express ER and PR, especially in cases such as inflammatory nasal polyps.⁵⁸

Clinical observations suggest that anaphylaxis is more common and severe in women compared with men. Hox et al⁵⁹ studied the effect of estrogen in a mice anaphylaxis model and found no evidence for an effect of ER on an Fc receptor I (high affinity IgE receptor)-mediated MC response. This indicates that

		Estrogen	Progesterone	Androgen
Nitric oxide (NO)		↗		
Mast cells	Density and/or Activation	↗	↘	→
Kallikrein-Kinin system				
	C1Inhibitor	↘		↗
	Plasminogen	↗		
	Factor XII	↗		
	Bradykinin	↗		

FIGURE 1. The influence of sex hormones on mast cells and the kallikrein-kinin system.

the estrogen-mediated potentiation of anaphylaxis occurs subsequent to MC activation, perhaps through estrogen-enhanced endothelial nitric oxide (NO) synthase tissue expression and NO production.⁵⁹

Female sex hormones appear to have an impact on MC number and their activation or maturation in many tissues and organ systems. This impact varies depending on the state of MC preactivation and the levels of other hormones such as PR. Mast cells also appear to have an important role in fertility and pregnancy.

Kallikrein-kinin system and female sex hormones

The kallikrein-kinin (KK) system is involved in HAE with or without C1-inhibitor (C1Inh) deficiency. Estrogen and androgen are involved in the control of this system through classical nuclear genomic actions or nongenomic effects at the membrane level or in the cytoplasm on various kinases. Various sites of transcription activation are targets for E2: ER-responsive elements (EREs) are the most specific.⁶⁰ The coagulation activation reflects the estrogenic activity at the hepatic level. Estrogens can interact with most steps of the KK cascade described subsequently and illustrated in Figure 1.

Factor XII. Estrogen-responsive elements can participate in activating the FXII pathway.⁶¹ Furthermore, increased plasma FXII levels has been reported using functional and immunologic assays in women taking OCPs.⁶²

Kallikrein. Potential EREs have been reported in the proximal promoter of rat KLK1, but their functional role(s) are unknown.⁶³

Plasminogen. Oral E2 is associated with an increase in plasminogen level.⁶⁴

C1-inhibitor. Estrogens were reported to decrease C1Inh levels in normal users during pregnancy and in women using OCPs.⁶⁵⁻⁶⁹ Although no effect of ERE on the C1Inh promotor gene has been identified, this does not exclude control at the transcriptome level. In contrast, an androgen-responsive element was identified in the promotor gene region of C1Inh, which upregulated the level of C1Inh.⁶³

TABLE I. Comparison of cyclic hypersensitivity disorders

Condition	Clinical presentation	Onset in relation to menstrual cycle	Diagnosis	Treatment options
Progestin hypersensitivity	Localized cutaneous symptoms with or without systemic noncutaneous symptoms that are variable but include anaphylaxis	Peak progesterone levels during luteal phase, which is 3-10 days before onset of menses; typically resolves 2-3 days into cycle but may persist throughout cycle	History; progesterone skin prick and patch skin testing unreliable; <i>in vitro</i> assay for specific immunoglobulin E to progesterone reported a sensitivity, specificity, positive predictive and negative predictive values of 82%, 100%, 86%, and 100%, respectively; progesterone challenge but associated with unnecessary morbidity	Avoidance of progesterone containing oral contraceptives; H1-antihistamines; selective estrogen receptor modulator drug (tamoxifen); 17 α -alkylated steroids (ie, danazol or stanozolol); suppression of menstrual cycle; desensitization to hormone without or with omalizumab; rarely (in extreme cases) bilateral oophorectomy
Catamenial hypersensitivity	Dermatitis, urticaria, angioedema, asthma, anaphylaxis usually in luteal phase of menstruation	Correlates with postonset of menstrual cycle when progesterone and estrogen levels decline	History; no diagnostic tests available	Treatment with nonsteroidal anti-inflammatory drugs to inhibit prostaglandins may be effective in some women; rarely (in severe cases) bilateral oophorectomy
Estrogen hypersensitivity	Presents as urticaria or delayed-type dermatitis	Premenstrual cycle	History; immediate and delayed hypersensitivity testing can demonstrate estrogen sensitization; confirmation by estrogen challenge	Stop estrogen containing oral contraceptives or hormone replacement therapy; progestin-only contraceptive; suppression of estrogen with estrogen antagonists (leuprolide acetate) or estrogen receptor antagonists (tamoxifen); rarely oophorectomy
Lactation-associated hypersensitivity	Anaphylaxis	A few days postpartum	History; skin testing to lactation hormones not useful	Symptoms resolve after stopping breastfeeding; if persistent, may respond to lactation suppression with bromocriptine

Bradykinin. Estradiol increases the production of BK through cleavage of high molecular weight kininogen (HMWK) and decreases its degradation by the inhibition of angiotensin converting enzyme (ACE) activity.^{62,70} It was demonstrated in animal models and humans that menopause treatment with E2 inhibits ACE activity while increasing the density of BK2 receptor (BK2R) and function.⁷¹ Bradykinin mediates vascular relaxation through the release of NO; moreover, E2 is a potent regulator of NO release, which further increases vasodilatation.⁷²

Progesterone also regulates tissue K in breast and endometrial cells.⁶³ A potential PR-responsive element is present in the promoter gene region of some tissue K. Aminopeptidase expression was previously reported to be increased by PR in hepatocytes.⁷³

Conversely, the KK system seems to have a role in gestation. The urinary excretion of K increases between gestational weeks 8 and 12 and decreases thereafter.⁷⁴ Vascular endothelial growth factor (the main factor regulating angiogenesis during pregnancies) and BK receptors interact with each other to magnify their vascular effects.⁷⁵ In guinea pig models and humans, immunohistochemical expression of BK2 receptor and K was observed in uteroplacental interfaces.⁷⁵⁻⁷⁸ Finally, alteration in the KK system has been shown in preeclampsia. Reduced urinary K levels are observed in hypertensive and intrauterine growth-restricted pregnancies.⁷⁹ At 16 weeks, the ratio of K to creatinine was shown to be one of the best predictors of preeclampsia. In addition, changes in angiotensin II receptor and BK2R may also be associated with preeclampsia.⁸⁰

There is evidence that female sex hormones influence the KK system, but gaps in knowledge remain about their pathophysiologic mechanisms.

CLINICAL EFFECTS OF SEX HORMONES MANIFESTING AS CYCLIC HYPERSENSITIVITY AND ANAPHYLAXIS

Sex hormones likely have a significant role in patients with CSU, because more women than men are affected with this condition. Pathogenic explanations for their role in CSU, such as sex hormone receptors expressed on MCs, were discussed earlier. Unlike HAE, the role of sex hormones in causing CSU is not as well-defined. Clinically, their most obvious effects are illustrated as cyclic hypersensitivity conditions that often present with a spectrum of cutaneous and systemic symptoms ranging from isolated CSU with or without AE to anaphylaxis. The following discussion regarding the most common forms of sex hormone-induced cyclic hypersensitivity and anaphylaxis, listed in Table I, provides insight into their potential, often unrecognized impact on CSU.

Progesterone hypersensitivity

Progesterone hypersensitivity (PH) typically presents with localized cutaneous manifestations, with or without systemic noncutaneous signs, which can be variable. Cutaneous eruptions^{81,82} can include maculopapular rashes, papules and plaques,^{83,84} eczematous dermatitis,^{2,1,22} urticaria with or without AE,⁸⁵⁻⁹⁰ vesiculobullous and/or vesiculopustular lesions,^{83,91} petechiae and purpura,^{92,93} stomatitis,^{94,95} vulvovaginal pruritus,⁹⁶ erythema multiforme,^{97,98} fixed drug eruption,^{99,100} or Stevens-Johnson syndrome,^{101,102} Systemic¹⁰³ anaphylaxis involving lip and facial AE, bronchospasm, and hypotension

temporally related to taking a PR containing contraceptive has been reported.¹⁰⁴ Spontaneous symptom onset can occur anytime between menarche to menopause. Some patients attributed the onset of PH to pregnancy or to previous exposure to exogenous progestogens alone or in combination with increased PR levels during menses. For reactions to endogenous PR, the patient's symptoms begin with peak PR levels during the luteal phase, which is 3 to 10 days before the onset of menses, but they may persist throughout the cycle.^{104,105} In women with irregular cycles, cyclical patterns can be difficult to identify and correlate with the luteal PR surge.⁸⁵ Women with PH will note symptoms related to exposure to oral exogenous progestin or progestin elution from an *in utero* device without correlation to the menstrual cycle.

The diagnosis of PH is difficult to confirm by PR skin testing owing to its unreliable nature, because PR formulations are suspended in oils, which may cause an irritant response. A recent *in vitro* enzyme-linked immunosorbent assay PR-specific IgE assay reported a sensitivity, specificity, positive predictive, and negative predictive values of 82%, 100%, 86%, and 100%, respectively, using β -hexosaminidase mediator release assay results as the reference standard.¹⁰⁶ Progesterone patch testing has been attempted to assess for a T cell-mediated contact dermatitis in patients presenting with cyclic eczematous rashes, but the predictive value remains uncertain.¹⁰⁷ Patient sera collected during follicular and luteal phases of the menstrual cycle were used for autologous serum skin testing to confirm a diagnosis.¹⁰⁸ Another useful diagnostic modality is the PR challenge. However, this approach can result in significant reactions in some patients, leading to unnecessary morbidity. Suppression of the menstrual cycle with an agent that inhibits gonadotropin release is also often used to confirm a PH diagnosis.

The approach of PH treatment is tailored to individuals' symptoms and therapeutic goals. Management requires collaboration among multiple providers, including the patient's allergist or immunologist, dermatologist, and/or gynecologist, depending on the recommended treatment. Treatment can range from simple avoidance of the offending hormone to treatment with H1-antihistamines, use of the selective estrogen receptor modulator drug tamoxifen, 17 α -alkylated steroids (ie, danazol or stanozolol),^{94,97,109} suppression of the menstrual cycle, desensitization to the hormone, and, in extreme circumstances, total hysterectomy with bilateral oophorectomy. When taken daily, side effects from tamoxifen will induce an oligomenorrheic or amenorrheic state; however, long-term use is associated with significant side effects including thromboembolic events, hot flashes, and abnormal uterine bleeding. In addition, although medical or surgical oophorectomy is effective therapy for patients with severe PH refractory to other treatments,^{95,110-112} women should be cautioned about complications caused by estrogen deficiency, such as osteopenia or osteoporosis.

Progesterone desensitization should be considered in women with severe symptoms not controlled with standard therapy (ie, H1-antagonists and/or glucocorticoids) or the requirement for high-dose PR treatment for *in vitro* fertilization.^{86,89} These procedures should be performed in a facility where emergency therapy (ie, epinephrine) is readily available under the supervision of an experienced clinician. These protocols are discussed in more detail elsewhere.¹¹³⁻¹¹⁵ In situations in which patients are unable to tolerate PR desensitization, omalizumab has been

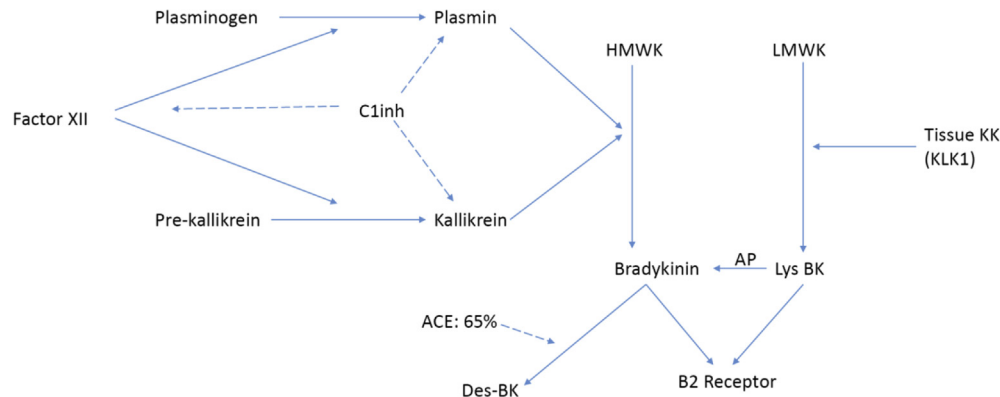


FIGURE 2. Kallikrein-kinin system involved in hereditary angioedema. *ACE*, Angiotensin converting enzyme; *AP*, aminopeptidase; *BK*, bradykinin; *HMWK*, high molecular weight kininogen; *KK*, kallikrein; *LMWK*, low molecular weight kininogen.

shown to attenuate or prevent these reactions so that desensitization can be successfully completed.¹¹⁶

Catamenial hypersensitivity

Catamenial anaphylaxis refers to symptoms of anaphylaxis that correlate with the time after the onset of the menstrual cycle when PR and estrogen levels decline, in contrast to PH, which occurs during the luteal peak before menstrual onset.¹¹⁷ However, the term catamenial anaphylaxis was also used in the literature to describe premenstrual PR responses, which can be confusing to the clinician.^{82,118} This condition is believed to be caused during the first day of the menstrual cycle by the release of prostaglandin F2 from the endometrium, which mediates uterine MC activation and the release of bioactive mediators, resulting in clinical symptoms.¹¹⁹⁻¹²¹ Thus, successful treatment with nonsteroidal anti-inflammatory agents such as indomethacin to inhibit prostaglandins was found to be effective in some women. Rarely, in severe cases, women have undergone a total hysterectomy with bilateral oophorectomy as treatment.¹¹⁹

Estrogen hypersensitivity

Estrogen hypersensitivity (EH) reactions¹²²⁻¹²⁷ are even rarer than PH and typically present as either a premenstrual urticaria eruption or delayed-type dermatitis.¹²³ Immediate and delayed hypersensitivity testing has been used to demonstrate estrogen sensitization confirmed by a positive estrogen challenge.^{123,124} Although the mechanism is poorly elucidated, it has been speculated to occur through a mechanism similar to that for other allergic reactions mediated by dendritic cells.¹²⁵ Women with EH taking an estrogen containing OCP may improve simply by stopping this therapy.¹²³ Otherwise, treatment is focused on suppressing estrogen using estrogen antagonists such as leuprolide acetate¹²⁶ or estrogen receptor antagonists such as tamoxifen.^{123,124} Women with EH also may respond to progestin-only contraceptives¹²⁷ and in severe rare cases have required an oophorectomy.¹²²

Lactation-associated anaphylaxis

Lactation-associated anaphylaxis is a rare condition associated with the manual expression of breast milk or actual breastfeeding; it usually begins a few days postpartum. In some cases, increased serum tryptase has been reported with breastfeeding-associated anaphylaxis.¹²⁸⁻¹³³ Speculated mechanisms for lactation-

associated anaphylaxis include a rapid decrease in PR that results in an increase in histamine release, anaphylaxis induced by nonsteroidal anti-inflammatory drugs used for postpartum pain control or hypersensitivity resulting from hormones, and oxytocin and prolactin involved in breast milk production and excretion, although previous skin testing to these hormones were negative in suspected patients.^{128,131,132} Lactation-associated hypersensitivity can reoccur with subsequent pregnancies.^{130,131} Usually symptoms resolve shortly after the woman stops breastfeeding, but if they are persistent, they may respond by suppressing lactation with bromocriptine.^{128,130,131}

CLINICAL EFFECT OF HORMONES IN WOMEN WITH HAE

Hereditary AE is a rare disease produced by mutations in different genes. The most representative form of HAE is that caused by C1Inh deficiency resulting from mutations in the *SERPINC1* gene (C1Inh-HAE).¹³⁴ Other HAE forms are related to mutations in the *F12*, *ANGPT1*, *PLG*, *KNG1*, *MYOF*, and *HS3ST6* genes and are known as FXII-HAE, ANGPT1-HAE, PLG-HAE, KNG1-HAE, MYOF-HAE, and HS3ST6-HAE.^{2,135} Finally, there are some family cases of AE without known mutations, called unknown-HAE.¹³⁶

Hereditary AE is characterized by recurrent localized swelling attacks in different locations (extremities, face, abdomen, upper airway, and so forth).¹³⁴ Bradykinin has been shown to be the main mediator in C1Inh-HAE and is also supposed to be involved in FXII-HAE.¹³⁷ Bradykinin is the result of activation of the KK system; it is formed by FXII, plasma prekallikrein (pK), and high molecular weight kininogen (HK). Activated FXII converts pK into plasma kallikrein (K), which cleaves HK and releases BK. Plasma K can also cleave activated FXII with the release of a smaller active protease, FXIIf. The fibrinolytic system can enhance BK production through plasmin activation of the KK system.¹³⁷ Finally, MASP-1, a protease from the lectin complement pathway, was involved in generating BK through direct HK cleavage.¹³⁸ Bradykinin binds BK2 receptor in endothelial cells, with subsequent phosphorylation of vascular endothelial cadherin and the release of NO, resulting in enhanced vascular permeability.¹³⁷ Fluid then leaks from the vascular space into the interstitial space and results in localized swelling.¹³⁷ Bradykinin has a short half-life and is quickly

TABLE II. Comparison of females and males with chronic spontaneous urticaria and hereditary angioedema types I and II

Characteristic	Chronic spontaneous urticaria	Hereditary angioedema type I/II
Prevalence	F > M	F > M
Genetics	?	F = M
Autoimmunity	F > M	?
Frequency of outbreaks or attacks	F > M	F > M
Sex hormone triggers	F > M	F > M

metabolized by ACE, plasma aminopeptidase P (APP), carboxypeptidase N and M, neutral endopeptidase, and dipeptidyl peptidase 4.¹³⁷

C1-Inhibitor inhibits several serine proteases of the complement system (C1r, C1s, MASP1, and MASP2), KKS (plasma KK, FXIIa, and FXIIb), coagulation FXIa, and plasminogen; thus, its deficiency favors excessive activation of the KKS and BK release in C1Inh-HAE.^{137,139} For its part, *F12* gene mutations in FXII-HAE, such as p.Thr309Lys, have been shown to increase FXII susceptibility to activation by plasmin.⁶ These mutations introduce new cleavage sites for plasmin and produce increased susceptibility to FXII activation.¹⁴⁰ Therefore, the fibrinolytic system can increase BK production through plasmin activation of FXII and subsequent activation of the KK system.¹⁴⁰

The role of exogenous hormones on the pathogenesis of C1Inh-HAE and FXII-HAE is shown in Figure 2.⁶⁰

Estrogens

Although C1Inh-HAE and FXII-HAE are inherited in an autosomal dominant pattern,¹³⁴ most case series show that female patients have a higher frequency and more severe AE attacks compared with males,¹⁴¹⁻¹⁴⁴ which has been attributed to estrogen.^{143,145} A study in female patients with C1Inh-HAE showed that the frequency of AE attack correlated with estrogen levels.¹⁴⁴ In addition, 60% to 80% of HAE female patients experience an increase in disease activity while using estrogen OCPs.^{27,146,147} Finally, worsening of disease with estrogen exposure (pregnancy or estrogen treatment) was described in both C1Inh-HAE and FXII-HAE as well as other forms of HAE-normal associated genes that are autosomal dominant with variable penetrance, but it is more frequent in FXII-HAE.^{145,148,149} However, in general, the specific mechanisms for swelling and potential hormonal effects are poorly understood for these rare conditions.

Estrogens have been demonstrated to act on many pathways that result in BK release. They can act directly in the endothelial cell membrane¹⁵⁰ or through the transcription of several genes.¹⁵¹ Several EREs can contribute to activating several important sites involved in HAE pathways; one is 7ERE in FXII, which may participate in FXII activation.⁶¹

Increased plasma antigenic and functional FXII levels were found in women taking low-dose estrogen OCPs.⁶² Estradiol is also a potent regulator for the release of NO involved in vascular vasodilation⁷² through an ER membrane receptor in the caveolae.¹⁵² In addition, it was suggested that ER could have a positive effect on relaxation independent of NO.¹⁵³ Estrogen can also stimulate the release of heat shock protein 90, leading to conversion of the pK-HMWK complex into a K-HMWK complex and augmented BK generation.¹⁵⁴ In addition, oral micronized E2 was shown to increase plasminogen, which could activate the fibrinolytic system.⁶⁴ An increase in fibrinolysis

related to OCPs was later confirmed in healthy women.^{155,156} Moreover, BK2R expression and function is upregulated by estrogens⁷¹ and HRT (conjugated equine estrogen combined with medroxyprogesterone acetate orally) can decrease BK degradation by inhibiting ACE activity in postmenopausal women.⁷⁰ Finally, C1Inh levels were shown to be decreased in relation to increased estrogens during pregnancy and when estrogen-containing OCPs were taken.^{61,62,65-68}

Estrogens can increase BK production, decrease BK catabolism, increase BK2R expression and function, and decrease C1Inh, which together may explain the worsening of BK-induced AE observed with increased endogenous estrogens (pregnancy) or administration of exogenous estrogens. The estrogen-induced aggravation of HAE makes contraception or other procedures, such as *in vitro* fertilization, more difficult in HAE patients.¹⁴⁵

Androgens

Androgens increase serum C1Inh levels and decrease disease activity in C1Inh-HAE.³⁵ For years, they have been used as a main treatment for long-term prophylaxis in C1Inh-HAE.^{134,157} Although a potential androgen-responsive element was identified in the promoter region of the *C1INH* gene¹⁵⁸ and was assumed to be involved in the efficacy of androgens in C1Inh-HAE through enhanced C1Inh synthesis by the normal *C1INH* gene allele, there is little evidence to support this hypothesis.¹⁵⁹ An increase in the expression of C1Inh messenger RNA (mRNA) in mononuclear cells in patients taking the minimum effective dose of danazol¹⁶⁰ and an increase in the plasma levels of APP, an enzyme involved in BK catabolism,¹⁶¹ could explain danazol efficacy in C1Inh-HAE. Although androgens were effective for long-term prophylaxis in some HAE patients, they are no longer recommended as first-line treatment owing to their adverse side effects and the development of targeted HAE therapies for long-term prophylaxis with fewer safety and toxicity concerns.

Progesterone and progestins

Progestin contraception is efficacious in females with HAE.^{146,147} This effect could be related to the inhibition of estradiol's effects on BK¹⁶² and increased APP expression in hepatocytes.¹⁶³

Prolactin

Lactation has been associated with an increased number of AE attacks,¹⁶³⁻¹⁶⁵ which has been attributed to increased prolactin levels.¹⁴⁴

CONCLUSIONS

Sex hormones have an important mechanistic role in regulating pathways involved in histaminergic and nonhistaminergic CSU and AE. As a result, unsurprisingly, many clinical

characteristics of these conditions are more common in females compared with males (Table II). This effect is likely nonspecific for CSU or many forms of AE, because many other chronic diseases such as asthma are affected by sex hormones. The role of sex hormones has been better elucidated for HAE because they have been shown to have multiple effects including upregulation of FXII, an important activator of the K pathway. However, their role in the underlying pathogenesis for CSU is still poorly elucidated. Although there are sex hormone receptors on MCs, only a small number of women develop hives in response to OCPs or HRT. Furthermore, women only rarely develop specific IgE antibodies resulting in progestin hypersensitivity. Autoimmunity is clearly linked to CSU, which is more common in women. This suggests that sex hormones could act as adjuvants in activating or upregulating autoimmune pathways. This review has attempted to provide an overview of what is currently understood about the relation of sex hormones and urticaria and AE. There are still significant knowledge gaps in an understanding of their role in these conditions, which require further investigation.

Clinical Pearls

Chronic spontaneous urticaria is a relatively common disease with increasing prevalence and a distinct female preponderance.

Sex hormones have a modest effect on the disease course of CSU.

The importance of sex hormones predisposing females to develop CSU is best illustrated in the context of autoimmunity, which involves a complex network of genetic, microbial, and environmental factors.

For PR hypersensitivity, the patient's symptoms begin with peak PR levels during the luteal phase, which is 3 to 10 days before the onset of menses, but it may persist throughout the cycle.

Catamenial anaphylaxis correlates after the onset of the menstrual cycle, when PR and estrogen levels decline, in contrast to PH, which occurs during the luteal peak before menstrual onset and is believed to be caused by the release of prostaglandin F2 from the endometrium.

Treatment of cyclic hypersensitivity ranges from simple avoidance of the offending hormone to treatment with H1-antihistamines, suppression of the menstrual cycle, and, in extreme circumstances, total hysterectomy with bilateral oophorectomy. For PH, desensitization to the hormone with or without pretreatment with omalizumab has been demonstrated to be effective.

Endogenous and exogenous estrogens and prolactin can worsen the course of HAE in female patients by different mechanisms.

Progesterone or progestins, which have an effect opposite that of estrogens, have been effectively used as oral contraception by HAE patients. In many cases, this has also lessened the frequency and severity of attack.

Androgens also have the opposite effect of estrogens and were found early on to reduce HAE attacks, presumably by increasing C1Inh levels. This led to their use as prophylactic treatment for years.

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