



High Estrogen States in Hereditary Angioedema: a Spectrum

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Abstract

Sex differences have been well documented within hereditary angioedema (HAE) over the past several decades. Females often experience more frequent and more intense attacks compared to their male counterparts. Additionally, elevated estrogen levels—as seen in pregnancy and use of oral contraceptives—is a widely known trigger for angioedema attacks. In this review article, we will outline how estrogens’ downstream effects increase bradykinin, a potent vasodilator and key mediator of HAE. Estrogen-dependent HAE is a rare disorder that provides insight into the relationship between HAE and estrogens. Females affected by this subtype of HAE only experience attacks when under “high estrogen states,” such as during pregnancy and when taking exogenous estrogens (most commonly, oral contraceptives). This unique phenotype has been documented in individuals with an activating Factor XII mutation. Thus, based on this clear genotype-phenotype relationship, we conclude that Factor XII may be key in our understanding of estrogens’ role in HAE. Lastly, we propose that the sex differences seen in HAE be viewed as a spectrum from exacerbation to underlying genetic mutations in Factor XII.

Keywords Hereditary angioedema · Estrogens · Factor XII · Estrogen-dependent angioedema · Estrogen-associated angioedema

Abbreviations

HAE	Hereditary angioedema
HMWK	High molecular-weight kininogen
C1INH	C1 esterase inhibitor
ARB	Angiotensin receptor blockers
TXA	Tranexamic acid

Introduction

Angioedema involves cutaneous and mucosal swelling of loose connective tissue including, but not limited to, the lips, eyelids, mouth, throat, and gastrointestinal tract. Certain individuals who are predisposed to attacks due to mutations are categorized as having hereditary angioedema or HAE.

Recent reports have placed the prevalence of HAE at 1 in 50,000, although this condition is likely underreported due to diagnostic failure [1]. This failure to diagnosis can be attributed to the heterogeneity of HAE presentations: attacks can look different among people, and even within the same person, due to variables including location, frequency, intensity, duration, and even sex.

Hereditary angioedema should be of special consideration to clinicians as it can be life-threatening if attacks involve the larynx. Up to 50% of individuals afflicted with HAE will experience laryngeal edema at least once in their lifetimes [2]. Additionally, hereditary angioedema can cause significant anxiety among patients due to the condition’s episodic and somewhat unpredictable nature. Although many episodes do not have a clear antecedent trigger, the most commonly reported triggers of attack are trauma and emotional stress [3]. Of note, states of high estrogen levels have been associated with increased frequency and intensity of attacks [2, 4]. This phenomenon is termed *estrogen-associated angioedema* [4]. This review article will explore the role of estrogens in hereditary angioedema with a focus on pathophysiologic mechanisms.

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Angioedema Types and Pathophysiology

Hereditary angioedema can be classified into different types based on molecular status of C1 esterase inhibitor. The different types of angioedema are detailed in Fig. 1. Importantly, hereditary angioedema is bradykinin-mediated and distinct from mast cell-mediated angioedema which presents with urticaria [5]. Elevation of bradykinin can explain the clinical presentation of HAE, as this mediator is known to increase vascular permeability. The link between bradykinin and C1 esterase inhibitor is best explained through the kallikrein-kinin pathway as demonstrated in Fig. 2. Prekallikrein forms a complex with high molecular-weight kininogen (HMWK). Once prekallikrein is activated, the cleavage of this complex is responsible for the production of bradykinin. Furthermore, C1 esterase inhibitor (C1INH) is a dual-negative regulator of this pathway: it inhibits both the activation of prekallikrein and cleavage of HMWK to bradykinin. Thus, individuals with deficiency or dysfunction of C1 esterase inhibitor—type I and II HAE, respectively—have predisposition for angioedema attacks due to elevated levels of bradykinin [6].

Factor XII of the contact pathway is also a key regulator of the kallikrein-kinin pathway, promoting activation of prekallikrein. Historically, individuals with functional C1 esterase inhibitor activity that experience HAE were considered in a separate category, type III. Type III is now considered a misnomer and has widely been replaced by an all-inclusive group that includes those with a Factor XII activating mutation. Up to 25% of individuals with normal C1 esterase inhibitor activity can be explained by the FXII mutation [7]. This specific subtype of HAE is of particular interest in this review article, as estrogens are known to interact with Factor XII [8]. Additionally, estrogen-associated angioedema and estrogen-dependent angioedema, in which attacks are exacerbated by or only occur during high estrogen states respectively, are strongly correlated with Factor XII mutation [4].

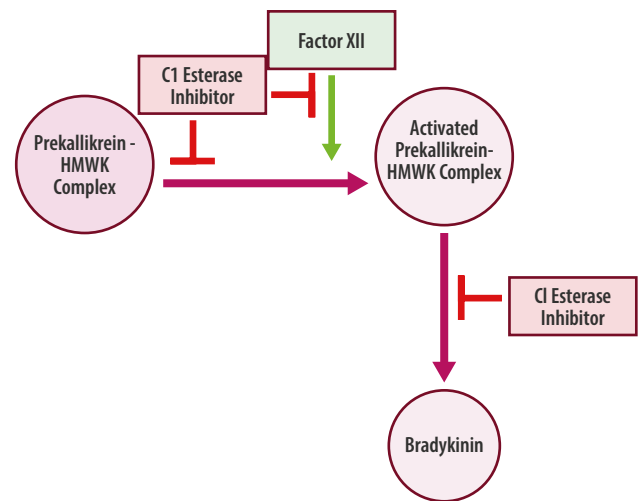


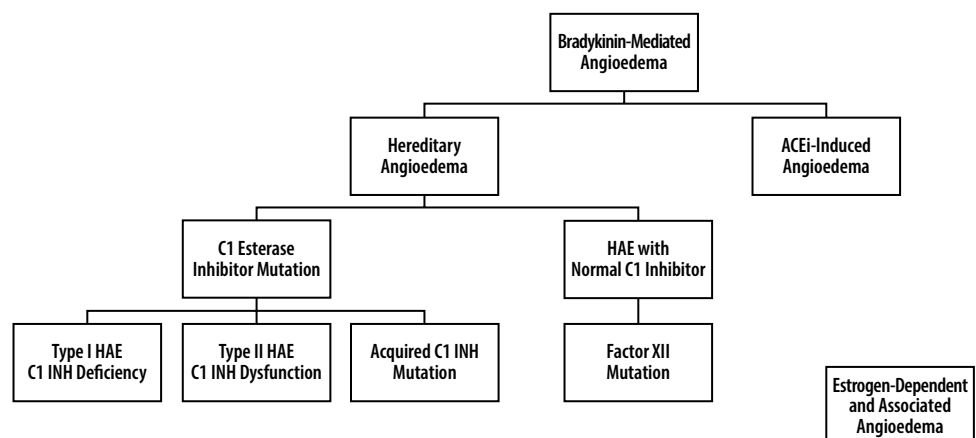
Fig. 2 Link between bradykinin and C1 esterase inhibitor best explained through the kallikrein-kinin pathway

Lastly, other forms of angioedema including acquired C1 esterase inhibitor mutations and ACE inhibitor-induced angioedema exist. The pathophysiology of ACE inhibitor-induced angioedema fits within the aforementioned paradigm as ACE is involved in bradykinin degradation.

Physiologic Effects of Estrogens

Estrogens are an intrinsic sex hormone responsible for the development of female sexual characteristics [9]. Furthermore, fluctuations in estradiol—the most potent and abundant of estrogens found during a woman's reproductive years—play an important role in menstruation and pregnancy. Although the physiology behind these complex high estrogen-state processes are beyond the scope of this review, understanding of the basic molecular pathway will aid greatly in our understanding of estrogens and HAE.

Fig. 1 Different types of angioedema



Estradiol binds intranuclear estrogen receptors α and β , which in turn alter transcription of genes through classical and non-classical pathways [9]. In the classical pathway, bound ER interacts with estrogen response elements on DNA while the non-classical pathway involves protein-protein interactions. In the context of menstruation, estrogens are produced by the follicles of the ovaries. Through the molecular pathway discussed above, these hormones will promote ovulation by leading to a surge of luteinizing hormone (LH). During pregnancy, the placenta contributes to production of estrogens; this hormone has been implicated in maintenance of pregnancy and parturition [10].

In addition to its physiologic role, estrogens also have therapeutic effects. Estrogens in combination with progesterone can effectively prevent ovulation by decreasing FSH and LH levels, thus preventing follicle maturation [11]. Estrogen therapy can also be used to supplement diminished hormone levels in menopausal women for symptomatic relief. Individuals with Turner syndrome, which is an essential state of hypogonadism, have also been treated with estrogen therapy to mimic normal pubertal development [12].

Estrogen therapy can also be used outside the scope of the female reproductive system. For example, estrogens' pharmacologic effects are vast, yet poorly understood. Evidence of estrogens' varied effects from immunologic to neoplastic are seen through its use as treatment in conditions like toxic shock syndrome and even prostate cancer [13, 14]. This understanding of estrogens' broad physiologic range leads us to our discussion of estrogens' role in hereditary angioedema.

High levels of estrogens have been implicated as a trigger for more frequent and intense attacks of angioedema [15]. Thus, a subset of HAE patients is women that experience exacerbation of attacks when pregnant or taking oral contraceptive; this condition is considered estrogen-associated angioedema. Furthermore, there is a smaller subset of HAE patients that only experience angioedema attacks during these states of high estrogens. As will be discussed in detail in the next section, there appears to be a complex spectrum of estrogens' influence on HAE, characterized by specific genetic mutations including Factor XII activating mutations. To further complicate this proposed spectrum, there appears to be a complex balance between sex hormones that dictates HAE presentation. While estrogens have been linked to worsening of the condition, androgen therapy, including danazol and stanozolol, has been used as an effective prophylactic treatment [16].

Sex Differences Within Hereditary Angioedema, a Spectrum

Clear sex differences exist within hereditary angioedema, contributing to the heterogeneity of the condition. For

example, ACE inhibitor-induced angioedema has been reported more frequently in the female sex [17]. Two cohort studies conducted by Toh et al. and Miller et al. performed a statistical analysis on a large sample size of patients taking ACE inhibitors and angiotensin receptor blockers (ARBs). Both studies found a statistically significant difference between males and females experiencing angioedema while on either ACE inhibitors or ARBs [18, 19].

Type I HAE has varied presentations between the sexes. Although this subtype of HAE follows an autosomal dominant inheritance pattern and affects both men and women equally, studies have shown that women often experience phenotypes with more intense and more frequent attacks compared to men [20]. Urs and colleagues have reported that within their cohort of patients with C1 esterase inhibitor deficiency, females experienced more symptoms and swelling episodes compared to their male counterparts. Additionally, women had more attacks to localized areas of the body like the abdomen, extremities, trunk, and face.

The most compelling evidence for sex differences of angioedema is the observation that estrogens are a known trigger for attacks. Increased frequency and intensity of attacks during states of high estrogen levels have been documented in all three hereditary angioedema types. These conditions include women that are taking oral contraceptives and estrogen therapy and those who are pregnant. When individuals who have previously been diagnosed with hereditary angioedema experience worsening symptoms during high estrogen states, this phenomenon is called *estrogen-associated* angioedema. By definition, these patients can experience attacks in the absence of increased estrogen levels. In contrast, *estrogen-dependent* angioedema describes a condition in which patients only experience attacks during high estrogen states; these individuals do not experience attacks once estrogen levels have returned to normal, for example, after gestation and after discontinuation of oral contraceptives.

Specific genetic mutations are correlated with estrogen-associated and estrogen-dependent hereditary angioedema. Individuals with Type I and II HAE with C1 esterase inhibitor mutations can experience estrogen-associated angioedema. Bouillet and colleagues demonstrated that within their cohort of women with a C1INH mutation, the majority showed worsening of disease with puberty and use of combined oral contraceptives; additionally, they describe a "hormone-sensitive phenotype" in which women that experienced severe symptoms during menses also experienced severe symptoms during pregnancy. A study by Bouillet et al. surveyed 150 post-pubertal women from 8 European countries with a C1 inhibitor enzyme activity level of 40% or lower or family or personal history of HAE. They found that 62% of individuals experienced exacerbated HAE during puberty. More specifically, 35% reported menses as a precipitating factor for attacks while

14% referenced ovulation. During pregnancy, 38% of women experienced more HAE attacks. However, the fact that 30% experienced fewer HAE attacks and 30% reported no effect during pregnancies suggests that the relationship between estrogens and HAE is not fully understood. This concept is further supported by the fact that 55% of those going through menopause had no change in HAE [21].

HAE with normal C1 esterase inhibitor activity, which has a clear predilection for the female sex, can lead to either estrogen-associated or estrogen-dependent angioedema. Of these cases, a subset has been identified to have Factor XII mutations. To our knowledge, based on case reports, the following Factor XII mutations have been described: Thr328Lys, Thr328Arg, and Thr309Lys, found on exon 9 of the Factor XII gene [4, 22, 23]. As will be discussed in the following pathophysiology section, estrogens are known to interact with Factor XII to increase bradykinin levels.

Although estrogen-dependent angioedema is a rare condition, isolated within a few familial pedigrees of European descent, it is of particular significance to this review article. Existence of the FXII subtype provides the most substantial indication that there is a connection between HAE and estrogens, as presentation of disease only occurs when estrogens are elevated. While those with Factor XII mutation within the documented pedigrees do not necessarily exhibit symptoms due to variable penetrance, to our knowledge, estrogen-dependent angioedema has only been demonstrated in individuals with a Factor XII mutation [4, 7, 22–24, 25]

Therefore, this relationship strongly suggests that estrogens' role in estrogen-dependent hereditary angioedema is mediated through Factor XII. Furthermore, estrogen-associated hereditary angioedema may have a similar pathophysiology as documented cases involve a Factor XII mutation. Lastly, Factor XII might explain some aspects of the estrogen-associated angioedema observed in Type I HAE, although further investigation is required and other factors may be involved as these individuals have not demonstrated Factor XII mutations.

We suggest that estrogens' influence on hereditary angioedema be viewed as a spectrum. Outlined in Fig. 3, we propose a novel classification to understand the various estrogen-associated and dependent angioedema subtypes seen in HAE. Moving across the spectrum from left to right, the subtypes of estrogen-related angioedema become more concretely linked to mutations that can explain the pathophysiology of the condition. Therefore, ACE inhibitor-induced angioedema constitutes the left side of the spectrum as attacks are triggered by use of medication, yet it is a finding seen more often in women. Estrogen-dependent angioedema that has only been documented in individuals with a Factor XII mutation is found on the right side of the spectrum as it delineates a clear relationship between estrogens, HAE, and Factor XII. Between the two extremes lies the estrogen-associated angioedema: Type I and II HAE in which individuals have C1INH dysfunction and the all-inclusive category of normal C1INH function that includes the subset of the Factor XII activating mutation. This spectrum will aid clinicians in diagnosing and treating patients that experience estrogen-triggered angioedema attacks.

Proposed Pathophysiology of Estrogen-Dependent and Associated Hereditary Angioedema

Molecular evidence helps to substantiate the claim that high estrogen states have the potential to trigger attacks in those affected by HAE. Estrogens strongly influence several key steps in the aforementioned kallikrein-kinin pathway. For example, the finding that women on oral contraceptives experience increased levels of plasma Factor XII and increased production through enhanced HMWK cleavage is well-documented [8]. Similarly, high estrogen states of pregnancy and the use of oral contraceptives have been reported to decrease the level of C1 esterase inhibitor. Estradiol is implicated in several other molecular pathways that could help explain its role in HAE. For example, estradiol is known to increase the release of nitric oxide, a potent vasodilator. Estradiol has also been shown to decrease

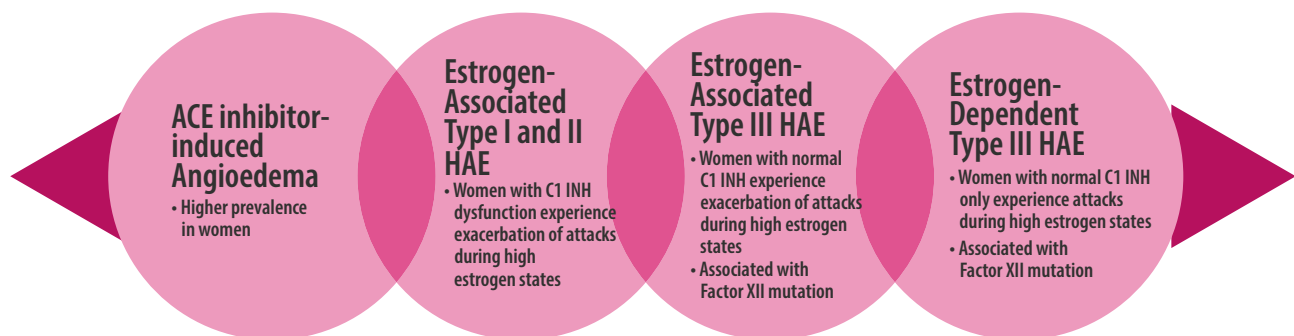


Fig. 3 Novel classification to understand the various estrogen-associated and dependent angioedema subtypes seen in HAE

Table 1 Assortment of hereditary angioedema cases reported in literature

Source	Mutations	Notes and trends	Management and outcomes
Hentges et al., <i>J Allergy Clin Immunol</i> 2009	1 of 4 patients had the Thr309Lys while authors could not identify mutation in other patients	4 patients experienced attacks while on OCPs, symptoms included swelling of extremities and pharynx - All patients had family history of attacks involving other female relatives	Authors did not discuss management of patients
Sanhueza, <i>American Society for Reproductive Medicine</i> , 2008	Type I HAE, decreased C1 esterase inhibitor concentration	- Female first presented with swelling of extremities and abdomen at 13 years old. Episodes of extreme abdominal pain occurred every 30 to 60 days - When started OCPs at age 18, episode frequency and intensity increased	- Given danazol - Advised to stop OCPs, given transdermal patch contraceptive as an alternative - After 26 months of suspension and treatment with transdermal contraceptive, patient had no symptoms or signs of angioedema
Bork et al., <i>J Allergy Clin Immunol</i> 2009, 124:129-34	13 families with missense mutation in Factor XII (p. Thr309Lys or p.Thr309Arg) - Normal C1 esterase inhibitor concentration and activity	- For most patients, clinical symptoms started in second decade of life - Majority of attacks involved skin, although abdominal pain, laryngeal edema, and tongue and uvula swelling were also reported - Mean frequency of angioedema attacks per symptomatic years was 12.7 - Although many attacks were brought on without known trigger, attacks could be associated with trauma, OCPs, pregnancy, and hormone replacement therapy	- Use of corticosteroids and anti-histamines were not effective for acute attacks - Prophylactic management through progesterone, danazol, and tranexamic acid proved highly effective
Picone et al., <i>Obstetrics and Gynecology International</i> , 2010	- Missense mutation of Factor XII, Thr328Lys identified in two families - Normal C1 esterase inhibitor concentration and activity	- Patient 1: 31-year-old female had history of 3 complicated pregnancies. First pregnancy resulted in ascites and spontaneous abortion of fetus. Second and third pregnancy associated with severe abdominal pain every 10 days. Abdominal pain occurred 2 days after swelling of face and extremities. Attacks only occurred when patient was using OCPs or was pregnant. Reported similar symptoms on her maternal side - Patient 2: 37-year-old Arab female. Presented during second pregnancy, while first ended in spontaneous first-trimester miscarriage of unknown cause. Reported facial, and laryngeal swelling and abdominal pain. Mother died during fourth pregnancy, likely due to laryngeal edema	- Article did not detail specific management of patients - Reported that emergent administration of C1 Inhibitor can be effective in some cases - Other options include androgens, tranexamic acid, kallikrein inhibitors and bradykinin receptor antagonists

Table 1 (continued)

Source	Mutations	Notes and trends	Management and outcomes
Deroux et al., Clinical and Experimental Immunology, 2016	57 patients from 24 different families with missense mutation in Factor XII (p. Thr309Lys or p. Thr309Arg) - Normal C1 esterase inhibitor concentration and activity	- Of 57 patients, 38 were symptomatic - Most patients described attacks of face, extremities and abdomen - Average age of first attack was 21 years 8 patients experienced attacks only during pregnancy or while on an OCP 24 patients had symptoms outside high estrogen-states, however pregnancy and use of OCPs exacerbated attacks	A cute episodes treated with tranexamic acid, C1-INH, and bradykinin receptor antagonists
Feray et al., International Journal of Obstetric Anesthesia, 2018	- Missense mutation of Factor XII, Thr328Lys - Normal C1 Esterase Inhibitor Concentration and Activity	32-year-old female that experienced repeated attacks during pregnancy, specifically of the abdomen and extremities - Experienced attacks before pregnancy, but aggravated during gestation	- Treated with tranexamic acid which reduced frequency of attacks during pregnancy - Prophylactic use of tranexamic acid postpartum was also effective

functionality of ACE, decreasing ACE-induced degradation of bradykinin [17]. Genetic analysis of the families that experience estrogen-dependent HAE due to an activating Factor XII mutation further confirms this relationship; for example, Cichon and colleagues performed enzymatic assays on members of a French family with the mutation, confirming that Factor XII-mediated substrate turnover was elevated, although increased bradykinin was not measured directly in these patients [22].

The above findings support the current paradigm that increased bradykinin is a key mediator in the pathogenesis of HAE. These changes in molecular profiles that occur during high estrogen states all result in a relative increase in bradykinin levels. Thus, it is consistent with the idea of estrogen-associated HAE: these individuals are predisposed to having more frequent and more intense attacks when experiencing high estrogen levels. Therefore, the threshold to trigger HAE attacks is lessened in these individuals as their baseline bradykinin levels are elevated compared to when they are not experiencing high estrogen states.

Summary of Case Reports

An assortment of case reports concerning estrogen-associated HAE is listed in Table 1. Of note are the ways in which these estrogen-associated and estrogen-dependent diseases were managed in these individuals. Patients were prophylactically given a combination of tranexamic acid (TXA), attenuated androgens like danazol, and bradykinin receptor antagonists like icatibant. These medications are also used in the management of type I and II HAE because they all work downstream of the defect, either Factor XII or C1 esterase inhibitor, improving the serum profile levels of bradykinin. Additionally, this explains why administration of C1 esterase inhibitor is beneficial in patients who have normal C1 esterase inhibitor concentration and function. Lastly, all acute symptomatic episodes that cause life-threatening laryngeal edema seen in any type of HAE are given a combination of corticosteroids and epinephrine.

Although management of the different types of HAE overlap extensively, it is important to identify the molecular defect as nuances in management do exist. Additionally, in patients who experience both estrogen-associated and estrogen-dependent HAE, clinicians can accurately inform patients of potential triggers like high estrogen states.

Future Directions

Estrogen-dependent angioedema provides a unique scenario in which we can understand the broad role of estrogens' effects in HAE. This is an example in which a clear genotype—an activating Factor XII mutation—dictates phenotype which provides compelling evidence implicating Factor XII as a key

mediator in the relationship between estrogens and HAE. As estrogen-dependent angioedema is a rare disorder that has only been documented in a few families, we suggest that future directions potentially include developing a preclinical (murine) model for estrogen-dependent angioedema through an activating Factor XII mutation. This model could not only provide important mechanistic insights, it can accelerate the development and testing of novel therapeutic strategies for this disease.

Furthermore, it is important to continue investigating this relationship between estrogens and HAE within the context of Factor XII. We can begin to apply this known relationship seen in estrogen-dependent angioedema to the more common subtypes of HAE: type I and II estrogen-associated HAE. Next steps in this investigation should include understanding whether parallels can be made between both estrogen-dependent angioedema and estrogen-associated angioedema. If such a relationship exists, then new treatments targeting Factor XII and the coagulation cascade might be considered in treating estrogen-related HAE.

Conclusion

Through addressing estrogens' pharmacologic effects on the bradykinin pathway, this review article elucidates several potential ways in which estrogens could predispose individuals to HAE attacks. More specifically, estrogen-dependent angioedema demonstrates that Factor XII is likely a key mediator in this relationship. Further investigation is required to understand whether Factor XII plays a similar role in the more common estrogen-associated angioedema. It is important to understand these relationships as high estrogen states might be difficult to avoid in individuals who are affected by HAE. A clear understanding of the pathogenesis, molecular pathways, and spectrum of sex differences seen in the complex and heterogeneous disorder is essential in developing effective counseling and treatment.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Abdulkarim A, Craig T (2020) Hereditary angioedema. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482266/>
2. Bernstein J (2018) Severity of hereditary angioedema, prevalence, and diagnostic considerations. *Am J Manag Care*. 24(14 Suppl):S292–S298. <https://pubmed.ncbi.nlm.nih.gov/30132643/> PMID: 30132643.
3. Nedelea I, Deleanu D (2019) Isolated angioedema: an overview of clinical features and etiology. *Exp Ther Med*. 17(2):1068–1072. <https://doi.org/10.3892/etm.2018.6982>. Epub 2018 Nov 16. PMID: 30679975; PMCID: PMC6327642.
4. Binkley K (2010) Factor XII mutations, estrogen-dependent inherited angioedema, and related conditions. *All Asth Clin Immun* 6:16. <https://doi.org/10.1186/1710-1492-6-16>
5. Misra L, Khurmi N, Terrence L (2016) Angioedema: classification, management and emerging therapies for the perioperative physician. *Indian J Anaesth* 60(8):534–541. <https://doi.org/10.4103/0019-5049.187776> PMID: 27601734; PMCID: PMC4989802
6. Liu J, Qin J, Borodovsky A et al (2019) An investigational RNAi therapeutic targeting factor XII (ALN-F12) for the treatment of hereditary angioedema. *RNA*. 25(2):255–263. <https://rnajournal.cshlp.org/content/early/2018/11/21/rna.068916.118>
7. Sharma J, Jindal BA et al (2021) Pathophysiology of hereditary angioedema (HAE) beyond the SERPING1 Gene. *Clinic Rev Allerg Immunol*. <https://doi.org/10.1007/s12016-021-08835-8>
8. Gompel A, Fain O, Boccon-Gibod I et al (2020) Exogenous hormones and hereditary angioedema *Int Immunopharmacol* 78 <https://doi.org/10.1016/j.intimp.2019.106080>
9. Nilsson S, Makela S, Treuter E et al (2001) Mechanisms of estrogen action. *Physiol Rev* 81(4):1535–1565. <https://doi.org/10.1152/physrev.2001.81.4.1535> (PMID: 11581496)
10. Sherman B, Korenman S (1974) Measurement of serum LH, FSH, estradiol and progesterone in disorders of the human menstrual cycle: the inadequate luteal phase. *J Clin Endocrinol Metab* 39(1):145–149. <https://doi.org/10.1210/jcem-39-1-145>
11. Baird D, Glasier A (1993) Hormonal contraception. *N Engl J Med* 328(21):1543–1549. <https://doi.org/10.1056/NEJM199305273282108> (PMID: 8479492)
12. Klein K, Rosenfield R, Santen R et al (2018) Estrogen replacement in turner syndrome: literature review and practical considerations. *J Clin Endocrinol Metab* 103(5):1790–1803. <https://doi.org/10.1210/jc.2017-02183>
13. Angele M, Pratschke S, Hubbard W et al (2014) Gender differences in sepsis: cardiovascular and immunological aspects. *Virulence* 5(1):12–19. <https://doi.org/10.4161/viru.26982>
14. Oh W (2002) The evolving role of estrogen therapy in prostate cancer. *Clin Prostate Cancer* 1(2):81–89. <https://doi.org/10.3816/cgc.2002.n.009> (PMID: 15046698)
15. Banerji A, Riedl M (2016) Managing the female patient with hereditary angioedema. *Womens Health* 12(3):351–361. <https://doi.org/10.2217/whe.16.6>
16. Zeerleder S, Levi M (2016) Hereditary and acquired C1-inhibitor-dependent angioedema: From pathophysiology to treatment. *Ann Med* 48(4):256–267. <https://doi.org/10.3109/07853890.2016.1162909>
17. Alharbi F, Kholod A, Souverein P et al (2017) The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: a case/noncase study in VigiBase. *Fundam Clin Pharmacol* 31(6):676–684. <https://doi.org/10.1111/fcp.12313>
18. Toh S, Reichman M, Houstoun M et al (2012) Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 172(20):1582–1589. <https://doi.org/10.1001/2013.jamainternmed.34>
19. Miller D, Oliveria S, Berlowitz D et al (2008) Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension* 51(6):1624–1630. <https://doi.org/10.1161/HYPERTENSIONAHA.108.110270>
20. Steiner U, Weber-Chrysochoou C, Helbling A et al (2016) Hereditary angioedema due to C1 - inhibitor deficiency in switzerland:

- clinical characteristics and therapeutic modalities within a cohort study. *Orphanet J Rare Dis* 11:43. <https://doi.org/10.1186/s13023-016-0423-1>
21. Bouillet L, Longhurst H, Boccon-Gibod I et al (2008) Disease expression in women with hereditary angioedema. *Obstet Gynecol* 199(5):484.e1–4. <https://doi.org/10.1016/j.ajog.2008.04.034> (Epub 2008 Jun 13 PMID: 18554570)
 22. Cichon S, Martin L, Hennies H et al (2006) Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet*. 79(6):1098–104. <https://doi.org/10.1086/509899>. Epub 2006 Oct 18. PMID: 17186468; PMCID: PMC1698720.
 23. Feray S, Fain O, Kayem G et al (2018) Repeated attacks of type III hereditary angioedema with factor XII mutation during pregnancy. *Int J Obstet Anesth* 36:114–118. <https://doi.org/10.1016/j.ijoa.2018.07.003> (Epub 2018 Aug 2 PMID: 30131260)
 24. Hentges F, Hilger C, Kohnen M et al (2009) Angioedema and estrogen-dependent angioedema with activation of the contact system *J Allergy Clin Immunol* 262–4 <https://doi.org/10.1016/j.jaci.2008.10.056> PMID: 19130939
 25. Deroux A, Boccon-Gibod I, Fain O et al (2016) Hereditary angioedema with normal C1 inhibitor and factor XII mutation: a series of 57 patients from the French national center of reference for angioedema. *Clin Exp Immunol* 185(3):332–337. <https://doi.org/10.1111/cei.12820>

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