Advances in Obstetrics and Gynecology Research, 2024, Volume 2, Issue 1
https://ojs.bbwpublisher.com/index.php/AOGR

Management of Hereditary Angioedema in Pediatric, Pregnant, and Breast-Feeding Patients: An Expert Opinion – A Secondary Publication

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Abstract: Hereditary angioedema (HAE) is a rare inherited condition marked by recurrent skin and submucosal edema. HAE is caused by a C1 inhibitor deficiency or decreased C1 inhibitor function. The initial attack may occur during childhood or pregnancy, with symptoms ranging from classic angioedema to nonspecific stomach cramps. In this review, we discuss strategies for children and pregnant women to manage HAE attacks effectively and safely in light of the recent increase in HAE diagnosis. To begin, an aggressive work-up is necessary to confirm HAE-1/2 and to determine the most effective countermeasures. Secondly, in the event of an acute attack, plasma-derived C1-inhibitor is the first line of defense for children and pregnant women. Icatibant is also appropriate for use, except in pregnant women. Fresh frozen plasma (FFP) may be suggested as an alternative. Thirdly, proactive measures to prevent HAE attacks should be considered whenever a procedure is performed that may result in an exacerbation. Finally, FFP, attenuated androgen, and antifibrinolytic agents

are recommended for long-term prophylaxis in South Korea where the C1 inhibitor is scarce. However, when making a decision, it is necessary to consider both the efficacy and the risk of adverse effects. For proper management, written action plans and first-aid kits are required. The action plans should be customized to the patient's unique circumstances.

Keywords: Hereditary angioedema; C1-inhibitor; Child; Pregnant; Breast-feeding

Online publication: February 28, 2024

1. Introduction

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent skin and mucosal swelling, which occurs due to deficiency or dysfunction of C1 esterase inhibitor (C1-INH). The severity of HAE varies widely, from asymptomatic to fatal, making it difficult to predict clinical outcomes and significantly impacting the daily lives of patients and their families.

More than half of patients experience their first symptoms during childhood or adolescence, requiring a differentiated approach to prevention and treatment for adults. Additionally, HAE is known to be influenced by factors such as stress, physical trauma, infection, and estrogen levels, which can affect the severity of acute attacks. Clinical courses in pregnant and breastfeeding women, who may experience increased hormonal levels, may differ from those of typical patients. Therefore, meticulous care from frontline healthcare providers is crucial for effective diagnosis and treatment in this patient population.

However, there is currently a lack of specialized literature focusing on children, pregnant women, and breastfeeding mothers domestically, and internationally, limited to a few reviews and case reports, posing significant challenges to clinical practice [1-6].

In response, healthcare professionals affiliated with the Korean Academy of Asthma, Allergy, and Clinical Immunology (KAAACI) who specialize in treating HAE have published expert opinions based on recent literature reviews and information [7]. This opinion paper aims to provide guidance for frontline clinicians, particularly regarding children, pregnant women, and breastfeeding mothers who require special consideration in managing HAE.

2. Definition and classification of HAE

To briefly summarize the overall classification of HAE for a better understanding of the content described in the primary expert opinion, the following points can be highlighted. Angioedema refers to swelling occurring in the deep dermis, subcutaneous tissue, mucosa, or mucosal tissue as local vascular permeability increases [8]. Based on the major mediators, angioedema is classified into histamine-mediated mast cell-mediated angioedema, bradykinin-mediated angioedema, and other types of angioedema that are difficult to clearly identify the cause [9]. Histamine-mediated angioedema mainly occurs as part of allergic reactions and is often accompanied by urticaria. In contrast, bradykinin-mediated angioedema occurs due to genetic or acquired deficiency of C1-INH and is mostly not accompanied by urticaria [10]. The HAE primarily addressed in this expert opinion belongs to bradykinin-mediated angioedema and is caused by genetic abnormalities.

HAE is classified into type 1 HAE, type 2 HAE, and normal C1-INH HAE based on genetic characteristics. Type 1 HAE is characterized by decreased levels of C1-INH, while type 2 HAE features normal levels of C1-INH but with functional impairment. Types 1 and 2 have similar mechanisms and clinical presentations, often collectively referred to as type 1/2 HAE. Type 1/2 HAE arises from mutations in the SERPING1 gene, which

encodes C1-INH, with over 700 different SERPING1 mutations reported to date [11]. Normal C1-INH HAE is very rarely encountered, and it is speculated that factors other than C1-INH are responsible for bradykinin receptor stimulation [12]. So far, six subtypes of normal C1-INH HAE have been reported [HAE due to factor XII gene (FXII) mutation (HAE-FXII); HAE due to angiopoietin-1 gene (ANGPT1) mutation (HAE-ANGPT1); HAE due to plasminogen gene (PLG) mutation (HAE-PLG); HAE due to kininogen-1 gene (KNG1) mutation (HAE-KNG1); HAE due to myoferlin gene (MYOF) mutation (HAE-MYOF); HAE due to heparan sulfate-glucosamine-3-O-sulfotransferase 6 gene (HS3ST6) mutation (HAE-HS3ST6)] [12]. Additionally, there are HAE cases where the exact causative gene is not known (HAE-UNK) [11].

3. HAE in Pediatrics

3.1. Clinical presentation and course of HAE in children

Mutations in the SERPING1 gene, which causes type 1/2 HAE, are present from birth, but the first symptoms typically manifest during childhood or adolescence. While there have been reported cases of symptoms appearing as early as 4 weeks after birth [13], such occurrences are extremely rare. According to large-scale studies in the United States, children with type 1/2 HAE experience their first attack at a median age of 11 years (range: 6–15 years), with a diagnosis typically occurring at around 19 years (range: 12–28 years), taking approximately 8 years (range: 1–16 years) from onset to diagnosis [14]. However, in Korea, the average age of initial symptom onset is 28 ± 14 years, with only about 26% experiencing their first attack before the age of 20 [15]. In children, attacks mostly present as cutaneous angioedema, which can be particularly dangerous in the pediatric airway due to its narrowness, potentially leading to asphyxiation [16]. Abdominal attacks are also rare in children, but due to the common occurrence of abdominal pain in this age group, it is difficult to accurately assess the true extent. The frequency and severity of attacks increase during adolescence, and the early onset of symptoms is associated with a more severe course of type 1/2 HAE [17]. Peripheral erythema is a common prodromal symptom in children, occurring in 42%–58% of all cases [11]. It is often misinterpreted as urticaria, leading to inaccurate and insufficient treatment [1,11,18,19].

3.2. Diagnosis of HAE in children

In situations where type 1/2 HAE is suspected, if angioedema occurs without erythema in children, it is recommended to measure the levels and activity of C1-INH antigen (protein) and C4 for diagnosis [11]. Since type 1/2 HAE follows an autosomal dominant inheritance pattern, children of affected patients have a 50% chance of inheriting the disease. Prompt testing is necessary for children of type 1/2 HAE patients, even if they currently do not exhibit clinical symptoms, to establish an optimal management plan [11,19,20]. Until all evaluations for type 1/2 HAE are completed, children of affected patients should be considered to have the disease and managed accordingly.

This consideration also applies to newborns. Until C1-INH deficiency is definitively ruled out, newborns should be considered to have the disease and cared for accordingly [11,20]. Interpretation of results requires attention due to the following factors: First, complement values measured using cord blood may yield false-negative results for HAE. Complement levels measured in cord blood are lower than those in maternal blood, with C1-INH levels in cord blood being only 70% and C1-INH activity being only 62% of those in adults [20,21]. Second, reference values for complement levels in pediatric peripheral venous blood are not yet established. However, it is known that C1-INH levels and activity are generally low in children with type 1/2 HAE, except in some exceptional cases in infants under 1 year old [22,23]. On the other hand, C4 levels can be low even in healthy infants, so diagnosing type 1/2 HAE based on decreased C4 levels in infants under 12

months old is not very helpful [22,23]. Third, genetic testing increases diagnostic reliability in children. Especially when biochemical test results are ambiguous, knowing the parents' genetic mutations can be very helpful in confirming the diagnosis of type 1/2 HAE through genetic testing [20,23]. However, genetic panels for HAE are not widely available in Korea, and some large hospitals only conduct them for research purposes. Due to the reasons mentioned above, all complement tests conducted initially in children of type 1/2 HAE patients should be repeated after the age of one [20,23].

Prenatal testing for type 1/2 HAE in fetuses during pregnancy is not recommended in clinical practice. The reasons include (1) the absence of observed mutations in the parents' C1-INH-related genes in many cases, up to about 10%, (2) even with the same mutation, phenotypes can vary significantly, and (3) advancements in treatment techniques have greatly improved disease control and quality of life for patients with type 1/2 HAE [24-26].

3.3. Treatment of HAE in pediatric patients

Just like in adults, it is essential to establish treatment guidelines in advance and have necessary emergency medications ready for all pediatric patients with type 1/2 HAE [11,27]. The approved emergency medications for pediatric patients with type 1/2 HAE are plasma-derived C1-inhibitor (trade name Berinert) and icatibant (trade name Firazyr). Recombinant C1-inhibitor (trade name Ruconest) is available as a rare drug for use in patients aged 13 and older, while ecallantide and Lanadelumab have not yet received approval in Korea. While all these medications are effective and safe for use, considering their availability in Korea, Icatibant is prioritized for use in adolescents and children under 12 years old [11]. Icatibant can be used in children aged 2 and older during acute attacks, with dosages based on weight. Icatibant is supplied in pre-filled syringes containing 30 mg in 3 mL, and the dosage is determined based on weight. Detailed recommended dosages are provided in **Table 1**. If Icatibant is unavailable, fresh frozen plasma (FFP) can be administered as an alternative [24,25]. Solvent-detergent-treated plasma is preferred over FFP, but both are considered second-line options [25]. Other available medications for pediatric use, their characteristics, and mechanisms of action are summarized in **Table 1** and **Figure 1**. In case of abdominal attacks, it is crucial to secure intravenous access and adequately replenish fluids. This is important as children are vulnerable to dehydration or hypovolemia, especially during HAE attacks involving leakage into the intestines or abdominal cavity [11].

Similar to adults, preventive measures for attacks are necessary before procedures. Medical, surgical, and dental procedures that can mechanically stimulate the upper airway or gastrointestinal tract fall under this category [28,29]. The primary consideration for preventive treatment is plasma-derived C1-inhibitor, administered at 15–30 units/kg. However, due to limited availability, attenuated androgens, such as danazol, at doses of 2.5–10 mg/kg/day (maximum 600 mg/day), may be considered as an alternative short-term option [20]. Androgens promote the synthesis of C1-INH protein, which is maintained by the expression of the remaining normal C1-related genes in the liver. Danazol is known to have increased efficacy with increasing doses, but individual doses required to prevent worsening of angioedema and maintain normal C1 and C4 levels vary significantly. Hence, it is recommended to adjust the dosage based on the response and side effects after starting the initial dose [27]. Since short-term preventive measures are not completely effective, emergency medications should also be available if needed [11].

Table 1. Treatment options available for HAE patients during pregnancy and breast-feeding

Drug	Route	Children			Pregnancy			Breast-feeding			Comments
		LTP*	STP	On-demand	LTP	STP	On-demand	LTP	STP	On-demand	
pdhC1INH†	IV	Y‡	Y‡	Y‡	Y‡	Y‡	Y‡	Y‡	Y‡	Y‡	Long-term prophylaxis requires individualized dosage intervals and doses.
FFP†	IV	(Y)	(Y)	(Y)	(Y)	(Y)	(Y)	(Y)	(Y)	(Y)	
AFs†	PO	(Y)	N	N	(Y)	N	N	(Y)	N	N	Efficacy is not proven. The suggested tranexamic acid dosage for children is 20–50 mg/kg.
rhC1INH†	IV	N	N	N	N	N	N	N	N	N	
AAs†	PO	(Y)	(Y)	N	N	N	N	N	N	N	The initial dose of danazol for children is 2.5 mg/kg per day. The advantages should exceed the risks of masculinization, hypogonadism, menstruation irregularities, and behavioral issues.
Icatibant†	SC	N	N	Y‡	N	N	N	N	N	N	Pediatric dosage is dependent on subjects' body weight: 12 to 25 kg, 10 mg (=1 mL); 26 to 40 kg, 15 mg (=1.5 mL); 41 to 50 kg, 20 mg (=2 mL); 51 to 65 kg, 25 mg (=2.5 mL); 65 kg and over, 30 mg (=3 mL). Isolated case reports of administration during pregnancy without adverse effects have been reported.
Ecallantide	SC	N	N	N	N	N	N	N	N	N	Approved only for adolescents in the US.
Lanadelumab	SC	N	N	N	N	N	N	N	N	N	Approved only for adolescents in the US.
Berotralstat	PO	N	N	N	N	N	N	N	N	N	

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; STP, short-term prophylaxis; pdhC1INH, plasma-derived C1-inhibitor; FFP, fresh frozen plasma; Afs, antifibrinolytics; rhC1INH, recombinant human C1 esterase inhibitor; AAs, attenuated androgens; IV, intravenous; SC, subcutaneous; PO, oral; Y, indicated; N, not indicated; (Y), only indicated if other drugs are not available. *This recommendation for LTP is confined to those aged under 12 years–for older children, follow the adult recommendation. †Available in Korea. ‡First choice.

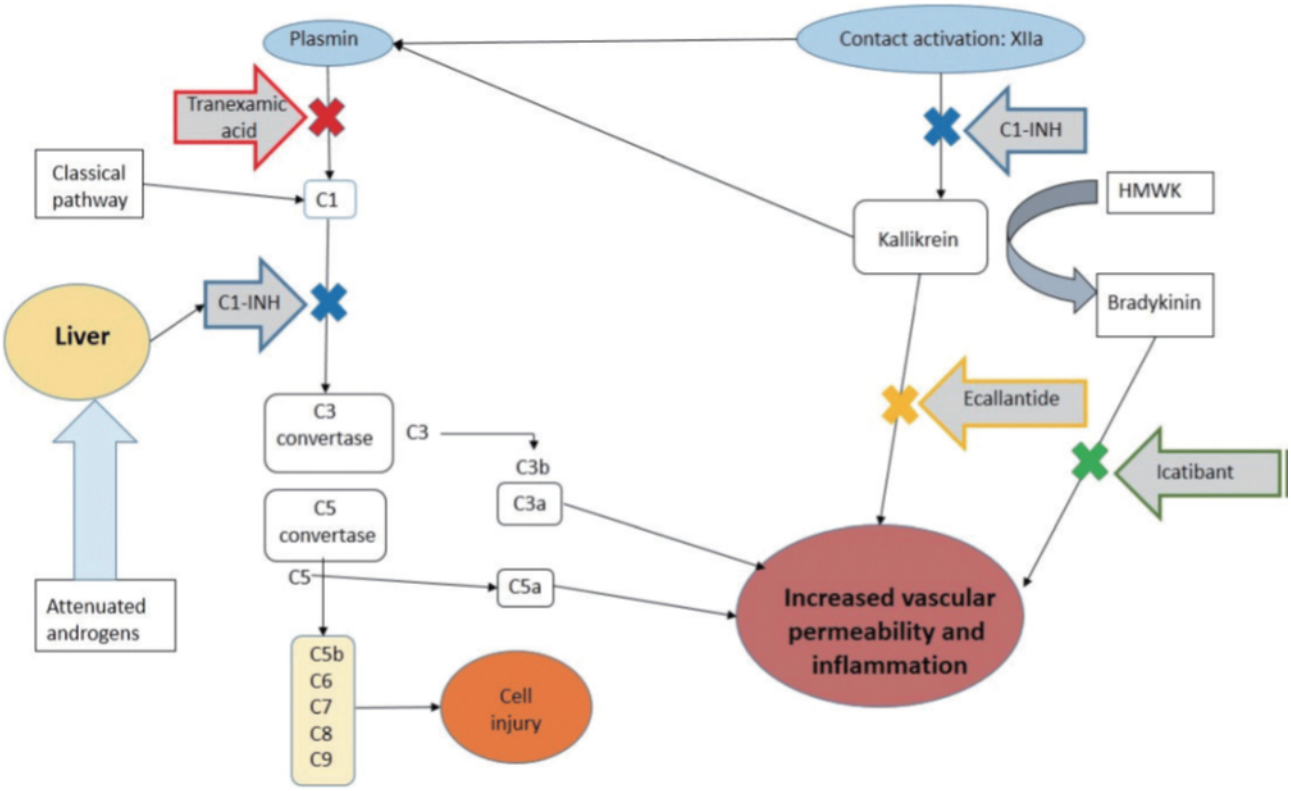

Figure 1. Targets and the action mechanisms of medications prescribed in children for managing their hereditary angioedema exacerbations [27]. Abbreviations: HMWK, high-molecular-weight kininogen.

The indications for long-term prophylactic therapy in adolescents are the same as those in adults [11]. Plasma-derived C1-inhibitor is recommended as the standard treatment for long-term prophylaxis in children under 12 years old, starting at 10–20 units/kg once or twice a week [20]. Subsequent dosing intervals and doses are adjusted based on individual responses to the medication [11]. However, considering the difficulty in obtaining C1-inhibitor in Korea, attenuated androgens or antifibrinolytics can be tried [11,19,20]. Antifibrinolytics inhibit the generation of plasmin, which is involved in the bradykinin pathway, without directly affecting C1-INH or C4 levels. Tranexamic acid is a representative antifibrinolytic, but due to the significant variability in the individual dose required to suppress symptoms, it is started at a low dose (20–50 mg/kg/day, divided into 2 or 3 doses) and adjusted based on the response and risk of side effects thereafter [27]. While using attenuated androgens may seem appropriate due to safety concerns with androgens being male hormones, the evidence supporting the efficacy of antifibrinolytics is still lacking. The safety of epsilon aminocaproic acid, another antifibrinolytic, compared to tranexamic acid is still unclear.

Close monitoring of safety indicators is necessary when administering attenuated androgens. These medications can cause virilization and hypogonadism in boys and menstrual irregularities in girls. They can also cause various behavioral abnormalities and may lead to premature closure of growth plates, potentially resulting in reduced final adult height [11,19,20]. Hence, attenuated androgens are not recommended for long-term prophylactic use in adolescents who have not reached Tanner stage V puberty and in all pediatric patients with HAE. It is important to periodically reassess the necessity of using attenuated androgens for long-term prophylaxis on a case-by-case basis and adjust the dosage and method of administration accordingly. For example, in the case of danazol, a representative attenuated androgen medication, the initial dose in children is

2.5 mg/kg/day, gradually increasing every 2 weeks. The dosage can be adjusted based on symptoms until the maximum recommended or tolerated dose (up to 200 mg once daily) is reached [11.20].

3.4. Considerations for primary prevention and management in pediatric HAE patients

In pediatric patients with type 1/2 HAE, most attacks occur without specific triggers [30], which is similar to adults. Infections are suspected as more common precipitating factors for attacks in children. Since essential vaccinations or recommended immunizations are safe, all should be administered. Preventing infections such as pharyngitis can reduce the frequency of attacks. Medications that can cause swelling as a side effect, such as ACE inhibitors, are not often necessary in children. However, in cases where oral contraceptives are required in children, contraceptive pills containing estrogen should be avoided as they can trigger HAE attacks [11,31]. On the other hand, intense physical activity accompanied by physical trauma or emotional stress, which are considered triggering factors in adults, are core exacerbating factors during childhood and adolescence [32]. However, overly restricting physical activity and lifestyle can be detrimental, so behavioral guidelines should be individualized according to the person's situation. The ultimate goal of managing type 1/2 HAE in all ages is for the patient to enjoy a safe and normal life [20,33].

In this context, providing appropriate information to pediatric patients and their families is essential for them to enjoy a healthy lifestyle and avoid complications [11]. It is important to provide information about this disease in document form to caregivers such as teachers and school nurses who handle children at daycare centers or schools. Among the information provided, management strategies for HAE attacks, including emergency treatment for respiratory attacks, must be included [11,19,20]. Ensuring that Icatibant is always available for emergency use at home, school, or during travel is essential. Guidelines for responding to attacks are needed, and emergency medications required for first aid should be available at home and local hospitals, with effective use of these medications included in the response plan [11]. While standardized forms for response plans are not yet well established, some countries are preparing for emergencies by providing standard forms for response plans from medical societies and having medical personnel describe detailed content for students to carry [34]. Since all HAE patients may potentially receive blood transfusions, it is advisable to administer hepatitis A and hepatitis B vaccinations if not already completed. Influenza vaccines and other essential vaccinations should also be administered if not yet completed. There are currently no recommendations regarding the COVID-19 vaccine, but based on reports targeting non-pregnant adult patients, many people were able to receive vaccinations well without short-term prophylactic therapy. Although some people experienced severe swelling as a side effect, they were able to manage acute exacerbations adaptively [35]. Based on these reports, it is recommended to proceed with the COVID-19 vaccination without short-term prophylactic therapy, and immediate response to acute exacerbations if necessary is recommended.

4. Pregnancy and breastfeeding in HAE

4.1. Clinical course of HAE during pregnancy and lactation

Anatomical, physiological, and hormonal changes during pregnancy can affect the symptoms of HAE and may impact the clinical course and treatment. Pregnancy can either alleviate or exacerbate the activity of HAE, or it may have no effect, and rarely, symptoms of angioedema may first appear during pregnancy. While the frequency of attacks observed during previous pregnancies can provide an estimate for the frequency of occurrence in subsequent pregnancies, accurate predictions are difficult [5,36-38]. Pregnant women with HAE require thorough and meticulous monitoring by specialists, and adjustment through close cooperation with experts in relevant fields is necessary. Labor and delivery rarely trigger attacks, but they can occur during

childbirth or within 48 hours postpartum, necessitating at least 72 hours of intensive observation even after uncomplicated vaginal delivery. Breastfeeding may be associated with an increase in attack frequency, such as abdominal symptoms or facial swelling, but breastfeeding is recommended based on the benefits of breastfeeding for the newborn [4,25]. In the case of cesarean section, especially when endotracheal intubation is required, it should be performed similarly to procedures performed on HAE patients described in the following sections.

4.2. Diagnosis of HAE during pregnancy

Due to an increase in plasma volume, plasma levels of C1-INH may decrease during pregnancy even in healthy women without HAE, and return to normal after delivery [39,40]. Therefore, measuring C1-INH, C1-INH activity, and C4 levels to diagnose type 1/2 HAE during pregnancy requires significant caution, and repeating tests after childbirth may be helpful for confirmation if HAE is suspected [4,25].

4.3. Treatment of HAE in pregnant and lactating women

C1-inhibitor (C1-INH) is recommended as first-line therapy for pregnant or lactating women with HAE due to its safety and high efficacy [11]. During pregnancy, medications such as Ecallantide, Lanadelumab, and Berotralstat are not indicated and have not been recommended as there have been no reported cases of their use to date. Although the use of Icatibant during pregnancy is contraindicated based on prescribing information, cases of its use during pregnancy have been reported without adverse effects on the mother or fetus [41-43]. If C1-INH is unavailable, fresh frozen plasma (FFP) may be considered as an alternative [5,36,37,44-46].

Prophylactic use of C1-INH is recommended before procedures that carry a risk of acute attacks during pregnancy, such as amniocentesis, cordocentesis, and termination of pregnancy surgery [4,11,25]. If prophylactic treatment is not administered before the procedure, immediate administration of C1-INH during the procedure is necessary, and if an attack occurs, it should be administered immediately. If managing acute attacks of HAE is difficult, it is advisable to give birth in a hospital where measures can be taken.

Although physical trauma or stress is known to trigger attacks, vascular swelling during labor or delivery is rare [5,25]. Therefore, while prophylactic treatment is not necessary for an uncomplicated vaginal delivery without complications, immediate administration of C1-INH concentrate should be available upon symptom onset. For patients who frequently experience swelling symptoms during the third trimester of pregnancy or have a history of genital swelling due to traumatic delivery or instrumental delivery [11,45-47], prophylactic administration of C1-INH concentrate before analgesia and delivery is recommended [11,37,44].

Preventive treatment may also be considered during pregnancy, especially for patients who have experienced an increase in the frequency of vascular swelling attacks during pregnancy. In such cases, plasma-derived C1-INH is recommended as a safe and effective preventive therapy [37]. Fibrinolytic inhibitors may be considered when C1-INH is not available, although their efficacy has not been proven [4,11,25]. Androgens are contraindicated during pregnancy because they pass through the placenta and can cause virilization of female fetuses, placental insufficiency, and fetal growth restriction. Androgen therapy must be discontinued before breastfeeding [48,49], as breastfeeding itself may reduce the frequency of attacks [37].

Plasma-derived C1-INH is recommended as the optimal treatment for symptomatic treatment, short-term prevention, and long-term prevention during lactation [11]. Androgens and fibrinolytic inhibitors are secreted in breast milk, but tranexamic acid has been shown to be safe during breastfeeding unlike androgens [50]. **Table 1** summarizes the types of medications that can be used during pregnancy and lactation [4,11].

4.4. Considerations for the management of pregnancy and childbirth in HAE patients

Type 1/2 HAE, although rare, can have a profound impact on the quality of life for patients and their families due to its unpredictable nature and potential lethality. Given the possibility of increased severity and acute exacerbation of HAE during pregnancy, systematic monitoring and maintenance therapy, as well as planning for acute symptoms, are paramount [4].

Expectant mothers diagnosed with type 1/2 HAE should receive management from healthcare professionals with sufficient knowledge, expertise, and experience in HAE. If diagnosed during pregnancy or with pre-existing HAE, it is essential to inform the obstetrician/gynecologist about the condition so that plans for short-term preventive treatment for acute attacks that may occur during surgery or procedures can be made in advance. Additionally, if long-term preventive therapy for pre-existing HAE is being conducted, consultation with the responsible specialist may be necessary to adjust medications, especially if taking drugs like attenuated androgens may be challenging to maintain during pregnancy. Moreover, caution is warranted regarding estrogen-containing oral contraceptives and estrogen hormone replacement therapy in relation to pregnancy planning, as they may exacerbate symptoms. Progesterone-only therapy for hormonal contraception may be beneficial for women with type 1/2 HAE [31,51].

Similar to general HAE patients, providing appropriate information about the condition and emergency response guidelines to patients and their families is essential for maintaining a normal life and preventing complications. Patients should have guidelines and medications for managing acute HAE attacks at home, and they should confirm and request emergency medications to be stocked by local emergency medical facilities.

5. Conclusion

Type 1/2 HAE, while rare, can significantly impact the quality of life and, if diagnosis is delayed, may lead to fatal outcomes. Although South Korea has a lower prevalence compared to Western countries, the difficulty in diagnosis suggests the possibility of undiagnosed patients, emphasizing the importance of early detection and appropriate treatment efforts. This statement hopes to contribute to such diagnosis and treatment efforts and further advocates for the domestic introduction of essential medications for optimal treatment of pediatric, pregnant, and lactating patients, who currently have a narrower range of treatment options.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Farkas H, Harmat G, Füst G, et al., 2002, Clinical Management of Hereditary Angio-Oedema in Children. Pediatr Allergy Immunol, 13(3): 153–161. https://doi.org/10.1034/j.1399-3038.2002.01014.x

[2] Boyle RJ, Nikpour M, Tang MLK, 2005, Hereditary Angio-Oedema in Children: A Management Guideline. Pediatr Allergy Immunol, 16(4): 288–294. https://doi.org/10.1111/j.1399-3038.2005.00275.x

[3] Johnston DT, Smith RC, 2020, Hereditary Angioedema: Special Considerations in Children. Allergy Asthma Proc, 41(Suppl 1): S43–S46. https://doi.org/10.2500/aap.2020.41.200042

[4] Caballero T, Canabal J, Rivero-Paparoni D, 2014, Management of Hereditary Angioedema in Pregnant Women: A Review. Int J Womens Health, 6: 839–848. https://doi.org/10.2147/IJWH.S46460

[5] González-Quevedo T, Larco JI, Marcos C, et al., 2016, Management of Pregnancy and Delivery in Patients with

Hereditary Angioedema Due to C1 Inhibitor Deficiency. J Investig Allergol Clin Immunol, 26(3): 161–167. https://doi.org/10.18176/jiaci.0037

[6] Shin M, Ahn K, 2013, A Case of Hereditary Angioedema in a 7-Year-Old Korean Girl. Allergy Asthma Immunol Res, 5(1): 59–61. https://doi.org/10.4168/aair.2013.5.1.59

[7] Jung JW, Park SY, Yoon SY, et al., 2022, Diagnosis and Treatment of Hereditary Angioedema: An Expert Opinion. Allergy Asthma Respir Dis, 10: 80–88.

[8] Bork K, Meng G, Staubach P, et al., 2006, Hereditary Angioedema: New Findings Concerning Symptoms, Affected Organs, and Course. Am J Med, 119(3): 267–274. https://doi.org/10.1016/j.amjmed.2005.09.064

[9] Maurer M, Magerl M, 2021, Differences and Similarities in the Mechanisms and Clinical Expression of Bradykinin-Mediated vs. Mast Cell-Mediated Angioedema. Clin Rev Allergy Immunol, 61(1): 40–49. https://doi.org/10.1007/s12016-021-08841-w

[10] Cicardi M, Zuraw BL, 2018, Angioedema Due to Bradykinin Dysregulation. J Allergy Clin Immunol Pract, 6(4): 1132–1141. https://doi.org/10.1016/j.jaip.2018.04.022

[11] Maurer M, Margerl M, Betschel S, et al., 2022, The International WAO/EAACI Guideline for the Management of Hereditary Angioedema – The 2021 Revision and Update. Allergy, 77(7): 1961–1990. https://doi.org/10.1111/all.15214

[12] Magerl M, Germenis AE, Maas C, et al., 2017, Hereditary Angioedema with Normal C1 Inhibitor: Update on Evaluation and Treatment. Immunol Allergy Clin North Am, 37(3): 571–584. https://doi.org/10.1016/j.iac.2017.04.004

[13] Bork K, Siedlecki K, Bosch S, et al., 2000, Asphyxiation by Laryngeal Edema in Patients with Hereditary Angioedema. Mayo Clin Proc, 75(4): 349–354. https://doi.org/10.4065/75.4.349

[14] Christiansen SC, Davis DK, Castaldo AJ, et al., 2016, Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. Clin Pediatr (Phila), 55(10): 935–942. https://doi.org/10.1177/0009922815616886

[15] Jung JW, Suh DI, Park HJ, et al., 2018, Clinical Features of Hereditary Angioedema in Korean Patients: A Nationwide Multicenter Study. Int Arch Allergy Immunol, 176(3–4): 272–279. https://doi.org/10.1159/000488350

[16] Bork K, Hardt J, Schicketanz KH, et al., 2003, Clinical Studies of Sudden Upper Airway Obstruction in Patients with Hereditary Angioedema Due to C1 Esterase Inhibitor Deficiency. Arch Intern Med, 163(10): 1229–1235. https://doi.org/10.1001/archinte.163.10.1229

[17] Martinez-Saguer I, Graff J, Rusicke E, et al., 2013, Does Early Clinical Manifestation of Hereditary Angioedema (HAE) Influence the Clinical Course of the Disease? J Allergy Clin Immunol, 131: AB30.

[18] Martinez-Saguer I, Farkas H, 2016, Erythema Marginatum as an Early Symptom of Hereditary Angioedema: Case Report of 2 Newborns. Pediatrics, 137(2): e20152411. https://doi.org/10.1542/peds.2015-2411

[19] Wahn V, Aberer W, Aygören-Pürsün E, et al., 2020, Hereditary Angioedema in Children and Adolescents – A Consensus Update on Therapeutic Strategies for German-Speaking Countries. Pediatr Allergy Immunol, 31(8): 974–989. https://doi.org/10.1111/pai.13309

[20] Farkas H, Martinez-Saguer I, Bork K, et al., 2017, International Consensus on the Diagnosis and Management of Pediatric Patients with Hereditary Angioedema with C1 Inhibitor Deficiency. Allergy, 72(2): 300–313. https://doi.org/10.1111/all.13001

[21] Grumach AS, Ceccon ME, Rutz R, et al., 2014, Complement Profile in Neonates of Different Gestational Ages. Scand J Immunol, 79(4): 276–281. https://doi.org/10.1111/sji.12154

[22] Aabom A, Andersen KE, Fagerberg C, et al., 2017, Clinical Characteristics and Real-Life Diagnostic Approaches in All Danish Children with Hereditary Angioedema. Orphanet J Rare Dis, 12(1): 55. https://doi.org/10.1186/s13023-017-0604-6

[23] Pedrosa M, Phillips-Angles E, Lopez-Lera A, et al., 2016, Complement Study Versus CINH Gene Testing for the Diagnosis of Type I Hereditary Angioedema in Children. J Clin Immunol, 36(1): 16–18. https://doi.org/10.1007/s10875-015-0222-9

[24] Pappalardo E, Caccia S, Suffritti C, et al., 2008, Mutation Screening of C1 Inhibitor Gene in 108 Unrelated Families with Hereditary Angioedema: Functional and Structural Correlates. Mol Immunol, 45(13): 3536–3544. https://doi.org/10.1016/j.molimm.2008.05.007

[25] Caballero T, Farkas H, Bouillet L, et al., 2012, International Consensus and Practical Guidelines on the Gynecologic and Obstetric Management of Female Patients with Hereditary Angioedema Caused by C1 Inhibitor Deficiency. J Allergy Clin Immunol, 129(2): 308–320. https://doi.org/10.1016/j.jaci.2011.11.025

[26] Germenis AE, Margaglione M, Pesquero JB, et al., 2020, International Consensus on the Use of Genetics in the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract, 8(3): 901–911. https://doi.org/10.1016/j.jaip.2019.10.004

[27] Salguero CAS, Chacon AIS, 2016, HAE in Children- What is the Best Treatment Strategy? Int J Aller Medications, 2(1): 016.

[28] Bork K, Hardt J, Staubach-Renz P, et al., 2011, Risk of Laryngeal Edema and Facial Swellings After Tooth Extraction in Patients with Hereditary Angioedema With and Without Prophylaxis with C1 Inhibitor Concentrate: A Retrospective Study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 112(1): 58–64. https://doi.org/10.1016/j.tripleo.2011.02.034

[29] Farkas H, Zotter Z, Csuka D, et al., 2012, Short-Term Prophylaxis in Hereditary Angioedema Due to Deficiency of the C1-Inhibitor – A Long-Term Survey. Allergy, 67(12): 1586–1593. https://doi.org/10.1111/all.12032

[30] Caballero T, Maurer M, Longhurst HJ, et al., 2016, Triggers and Prodromal Symptoms of Angioedema Attacks in Patients with Hereditary Angioedema. J Investig Allergol Clin Immunol, 26(6): 383–386. https://doi.org/10.18176/jiaci.0102

[31] Busse PJ, Christiansen SC, Riedl MA, et al., 2021, US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract, 9(1): 132–150.e3. https://doi.org/10.1016/j.jaip.2020.08.046

[32] Zotter Z, Csuka D, Szabo E, et al., 2014, The Influence of Trigger Factors on Hereditary Angioedema Due to C1-Inhibitor Deficiency. Orphanet J Rare Dis, 9: 44. https://doi.org/10.1186/1750-1172-9-44

[33] Farkas H, Varga L, Szeplaki G, et al., 2007, Management of Hereditary Angioedema in Pediatric Patients. Pediatrics, 120(3): e713–e722. https://doi.org/10.1542/peds.2006-3303

[34] Australasian Society of Clinical Immunology and Allergy, 2022, ASCIA HAE Position Paper and Management Plan, viewed 26 Mar 2022, https://www.allergy.org.au/hp/papers/hereditary-angioedema

[35] Fijen LM, Levi M, Cohn DM, 2021, COVID-19 Vaccination and the Risk of Swellings in Patients with Hereditary Angioedema. J Allergy Clin Immunol Pract, 9(11): 4156–4158. https://doi.org/10.1016/j.jaip.2021.08.039

[36] Czaller I, Visy B, Csuka D, et al., 2010, The Natural History of Hereditary Angioedema and the Impact of Treatment with Human C1-Inhibitor Concentrate During Pregnancy: A Long-Term Survey. Eur J Obstet Gynecol Reprod Biol, 152(1): 44–49. https://doi.org/10.1016/j.ejogrb.2010.05.008

[37] Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, et al., 2010, Characterization of Acute Hereditary Angioedema Attacks During Pregnancy and Breast-Feeding and Their Treatment with C1 Inhibitor Concentrate. Am J Obstet Gynecol, 203(2): 131.e1–7. https://doi.org/10.1016/j.ajog.2010.03.003

[38] Satomura A, Fujita T, Nakayama T, 2018, Comparison of the Frequency of Angioedema Attack, Before and During Pregnancy, in a Patient with Type I Hereditary Angioedema. Intern Med, 57(5): 751–755. https://doi.org/10.2169/internalmedicine.9407-17

[39] de Rojas DHF, Ibañez E, Longhurst H, et al., 2015, Treatment of HAE Attacks in the Icatibant Outcome Survey: An Analysis of Icatibant Self-Administration versus Administration by Health Care Professionals. Int Arch Allergy Immunol, 167(1): 21–28. https://doi.org/10.1159/000430864

[40] Ogston D, Walker J, Campbell DM, 1981, C1 Inactivator Level in Pregnancy. Thromb Res, 23(4–5): 453–455. https://doi.org/10.1016/0049-3848(81)90206-1

[41] Kaminsky LW, Kelbel T, Ansary F, et al., 2017, Multiple Doses of Icatibant Used During Pregnancy. Allergy Rhinol (Providence), 8(3): e178–e181. https://doi.org/10.2500/ar.2017.8.0210

[42] Farkas H, Kőhalmi KV, Veszeli N, et al., 2016, First Report of Icatibant Treatment in a Pregnant Patient with Hereditary Angioedema. J Obstet Gynaecol Res, 42(8): 1026–1028. https://doi.org/10.1111/jog.13003

[43] Zanichelli A, Mansi M, Periti G, 2015, Icatibant Exposure During Pregnancy in a Patient with Hereditary Angioedema. J Investig Allergol Clin Immunol, 25(6): 447–449.

[44] Galan HL, Reedy MB, Starr J, et al., 1996, Fresh Frozen Plasma Prophylaxis for Hereditary Angioedema During Pregnancy. A Case Report. J Reprod Med, 41(7): 541–544.

[45] Nathani F, Sullivan H, Churchill D, 2006, Pregnancy and C1 Esterase Inhibitor Deficiency: A Successful Outcome. Arch Gynecol Obstet, 274(6): 381–384. https://doi.org/10.1007/s00404-006-0183-6

[46] Caliskaner Z, Ozturk S, Gulec M, et al., 2007, A Successful Pregnancy and Uncomplicated Labor with C1INH Concentrate Prophylaxis in a Patient with Hereditary Angioedema. Allergol Immunopathol (Madr), 35(3): 117–119. https://doi.org/10.1157/13106781

[47] Farkas H, Csuka D, Tóth F, et al., 2012, Successful Pregnancy Outcome After Treatment with C1-Inhibitor Concentrate in a Patient with Hereditary Angioedema and a History of Four Miscarriages. Eur J Obstet Gynecol Reprod Biol, 165(2): 366–367. https://doi.org/10.1016/j.ejogrb.2012.07.010

[48] Brunskill PJ, 1992, The Effects of Fetal Exposure to Danazol. Br J Obstet Gynaecol, 99(3): 212–215. https://doi.org/10.1111/j.1471-0528.1992.tb14501.x

[49] Wentz AC, 1982, Adverse Effects of Danazol in Pregnancy. Ann Intern Med, 96(5): 672–673. https://doi.org/10.7326/0003-4819-96-5-672

[50] Gilad O, Merlob P, Stahl B, et al., 2014, Outcome Following Tranexamic Acid Exposure During Breastfeeding. Breastfeed Med, 9(8): 407–410. https://doi.org/10.1089/bfm.2014.0027

[51] Saule C, Boccon-Gibod I, Fain O, et al., 2013, Benefits of Progestin Contraception in Non-Allergic Angioedema. Clin Exp Allergy, 43(4): 475–482. https://doi.org/10.1111/cea.12055