

# International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency

Teresa Caballero, MD, PhD,<sup>a\*</sup> Henriette Farkas, MD, PhD, DSc,<sup>b\*</sup> Laurence Bouillet, MD, PhD,<sup>c\*</sup> Tom Bowen, MD,<sup>d</sup> Anne Gompel, MD, PhD,<sup>e</sup> Christina Fagerberg, MD,<sup>f</sup> Janne Bjökander, MD,<sup>g,†</sup> Konrad Bork, MD,<sup>h,†</sup> Anette Bygum, MD,<sup>i,†</sup> Marco Cicardi, MD,<sup>j,†</sup> Caterina de Carolis, MD,<sup>k</sup> Michael Frank, MD,<sup>l</sup> Jimmy H. C. Gooi, MD,<sup>m,‡</sup> Hilary Longhurst, MD,<sup>n,‡</sup> Inmaculada Martínez-Saguer, MD,<sup>o,‡</sup> Erik Waage Nielsen, MD,<sup>p,‡</sup> Krystina Obtulowitz, MD,<sup>q,‡</sup> Roberto Perricone, MD,<sup>r</sup> and Nieves Prior, MD<sup>a,‡</sup> Madrid, Spain, Budapest, Hungary, Grenoble and Paris, France, Calgary, Alberta, Canada, Odense, Denmark, Jönköping, Sweden, Mainz and Frankfurt/Mainz, Germany, Milan and Rome, Italy, Durham, NC, Leeds and London, United Kingdom, Bodø, Norway, and Krakow, Poland

**Background:** There are a limited number of publications on the management of gynecologic/obstetric events in female patients with hereditary angioedema caused by C1 inhibitor deficiency (HAE-C1-INH).

**Objective:** We sought to elaborate guidelines for optimizing the management of gynecologic/obstetric events in female patients with HAE-C1-INH.

**Methods:** A roundtable discussion took place at the 6th C1 Inhibitor Deficiency Workshop (May 2009, Budapest, Hungary). A review of related literature in English was performed.

**Results: Contraception:** Estrogens should be avoided. Barrier methods, intrauterine devices, and progestins can be used.

**Pregnancy:** Attenuated androgens are contraindicated and should be discontinued before attempting conception. Plasma-derived human C1 inhibitor concentrate (pdhC1INH) is preferred for acute treatment, short-term prophylaxis, or long-term prophylaxis. Tranexamic acid or virally inactivated fresh frozen plasma can be used for long-term prophylaxis if human plasma-derived C1-INH is not available. No safety data are available on icatibant, ecallantide, or recombinant human C1-INH (rhC1INH). **Parturition:** Complications during vaginal

From <sup>a</sup>Servicio de Alergia, Hospital La Paz Health Research Institute (IdiPaz), Biomedical Research Network on Rare Diseases–U754 (CIBERER), Madrid; <sup>b</sup>the Faculty of Medicine, 3rd Department of Internal Medicine, Semmelweis University, Budapest; <sup>c</sup>the Department of Internal Medicine, Grenoble University Hospital; <sup>d</sup>the Department of Medicine and Pediatrics, University of Calgary; <sup>e</sup>University Paris Descartes, APHP, Unité de Gynécologie Endocrinienne, Paris; <sup>f</sup>the Department of Clinical Genetics, Odense University Hospital; <sup>g</sup>the Department of Internal Medicine, County Hospital Ryhov, Jönköping; <sup>h</sup>the Department of Dermatology, University Hospital of the Johannes Gutenberg University of Mainz, Mainz; <sup>i</sup>the Department of Dermatology and Allergy Centre, Odense University Hospital; <sup>j</sup>Dipartimento di Scienze Cliniche Luigi Sacco, Milan; <sup>k</sup>Gynaecology and Obstetrics II, Azienda Ospedaliera San Giovanni-Addolorata, Rome; <sup>l</sup>Duke University Medical Center, Durham; <sup>m</sup>the Department of Immunology, St James's University Hospital, Leeds; <sup>n</sup>the Department of Immunology, Barts and the London NHS Trust, London; <sup>o</sup>Johann Wolfgang Goethe University, Frankfurt/Mainz; <sup>p</sup>the Department of Anesthesiology, Norland Hospital, Bodø; <sup>q</sup>Jagiellonian University Hospital, Krakow; and <sup>r</sup>Rheumatology, Allergology and Clinical Immunology, Department of Internal Medicine, University of Rome Tor Vergata, Rome.

\*These authors contributed equally to this work.

†Budapest HAE-C1-INH Study Group for Management of Female Patients (in alphabetical order).

§PREHAEAT Group (in alphabetical order).

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Corresponding author: Teresa Caballero, MD, PhD, Servicio de Alergia, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain. E-mail: [teresa.caballero@idipaz.es](mailto:teresa.caballero@idipaz.es).

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delivery are rare. Prophylaxis before labor and delivery might not be clinically indicated, but pdhC1INH therapeutic doses (20 U/kg) should be available. Nevertheless, each case should be treated based on HAE-C1-INH symptoms during pregnancy and previous labors. pdhC1INH prophylaxis is advised before forceps or vacuum extraction or cesarean section. Regional anesthesia is preferred to endotracheal intubation. **Breast cancer:** Attenuated androgens should be avoided. Antiestrogens can worsen angioedema symptoms. In these cases anastrozole might be an alternative. Other issues addressed include special features of HAE-C1-INH treatment in female patients, genetic counseling, infertility, abortion, lactation, menopause treatment, and endometrial cancer.

**Conclusions:** A consensus for the management of female patients with HAE-C1-INH is presented. (J Allergy Clin Immunol 2012;129:308-20.)

**Key words:** Angioedema, breast cancer, C1 inhibitor deficiency, contraception, delivery, fertility, genetic counseling, hereditary angioedema, pregnancy, treatment

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Hereditary angioedema (HAE) caused by C1 inhibitor (C1-INH) deficiency (HAE-C1-INH) is a rare disease,<sup>1</sup> with an estimated prevalence of between 1:10,000 and 1:50,000.<sup>2</sup> A minimal prevalence of between 1.09 and 1.41 per 100,000 inhabitants has been reported.<sup>3,4</sup> HAE-C1-INH is classified as 2 phenotypic variants<sup>5</sup>: subtype I (85%) is characterized by low levels of C1-INH protein, and subtype II (15%) has normal or high C1-INH levels, which is dysfunctional. The genetic defect is inherited as a Mendelian autosomal dominant trait.<sup>1</sup>

C1-INH regulates activation of the complement, contact, and intrinsic coagulation systems. Bradykinin, a vasoactive peptide responsible for increased vascular permeability, is the main mediator.<sup>6-9</sup>

Clinical symptoms consist of transient, well-circumscribed, nonpruritic swellings of the deep cutaneous, subcutaneous, or submucous tissue. Subcutaneous edema can appear on the extremities, face, torso, neck, and genitals and if left untreated usually resolves itself within several days. Attacks involving the gastrointestinal mucosa might appear to be a surgical emergency and sometimes lead to unnecessary laparotomy.<sup>10-12</sup> Upper airway edema can result in death from asphyxia.<sup>13-15</sup> Patients with HAE-C1-INH are at particular risk of upper airway edema in the case of dental manipulations, orofacial surgical interventions,<sup>16,17</sup> and some medical procedures, such as endoscopy and bronchoscopy.

Clinical expression is variable, and female patients are usually more severely affected. Estrogens can worsen the course of the disease<sup>18-22</sup> and present problems for managing contraception, pregnancy, *in vitro* fertilization (IVF), and menopause. Although consensus approaches have been published on the diagnosis and management of patients, aspects of special importance for female patients have not been fully addressed.<sup>23-26</sup> There is a lack of literature on how to handle gynecologic/obstetric events in female patients with HAE-C1-INH, although some series on the management of pregnancy have been reported.<sup>27-29</sup>

In this article guidelines have been developed for the management of gynecologic and obstetric events in women with hereditary HAE-C1-INH.

#### Abbreviations used

AA:	Attenuated androgen
C1-INH:	C1 inhibitor
FFP:	Fresh frozen plasma
HAE:	Hereditary angioedema
HAE-C1-INH:	Hereditary angioedema caused by C1 inhibitor deficiency
IUD:	Intrauterine device
IVF:	<i>In vitro</i> fertilization
LTP:	Long-term prophylaxis
MPA:	Medroxyprogesterone acetate
pdhC1INH:	Plasma-derived human C1 inhibitor concentrate
PGD:	Preimplantation genetic diagnosis
POP:	Progesterone-only pill
PREHAEAT:	European Concerted Action "Novel Methods for Predicting, Preventing and Treating Attacks in Patients with Hereditary Angioedema"
STP:	Short-term prophylaxis
TA:	Tranexamic acid
viFFP:	Virally inactivated fresh frozen plasma

## METHODS

### Bibliographic search

A comprehensive search of available English-language literature was carried out on PubMed using the following key words: "hereditary angioedema," "C1 inhibitor deficiency," and "C1 inhibitor." Additional references were identified from the reference lists of published articles. Searches were last updated on September 30, 2010. Additional data were obtained from abstracts known to the authors but not listed in PubMed. All publications consulted were reviewed for data related to the management of female patients.

### Discussion

An expert panel meeting and a roundtable discussion took place during the 6th C1 Inhibitor Deficiency Workshop in Budapest in May 2009 ([www.haenet.hu](http://www.haenet.hu)). Gynecologists and geneticists with experience in HAE-C1-INH provided their analysis. Areas in which published scientific data were insufficient were outlined for further review.

### Evidence level

When appropriate, the levels of evidence available to support the views expressed in this document have been indicated as in Table I, in accordance with US Preventive Services Task Force Guidelines for ranking evidence on the effectiveness of treatments or screening.<sup>30</sup>

## RESULTS

### 1. Gynecologic symptoms

**Genital edema.** Female patients with HAE-C1-INH can have genital edema. Horse riding, bike riding, or sexual intercourse can precipitate attacks.

### 2. Special features of HAE-C1-INH treatment in female patients

Management can be divided into short-term prophylaxis (STP) and long-term prophylaxis (LTP) and acute treatment. Available drugs for the treatment of patients with HAE-C1-INH can be seen in Table II.

**2.1. Acute treatment.** Edematous attacks can be effectively treated with plasma-derived human C1 inhibitor concentrate

**TABLE I.** Levels of evidence (US Preventive Services Task Force for ranking evidence about the effectiveness of treatments or screening)

Level	Description
I	At least 1 properly designed randomized controlled trial
II-1	Well-designed controlled trials without randomization
II-2	Well-designed cohort or case-control analytic studies, preferably from more than 1 center or research group
II-3	Multiple time series with or without the intervention Dramatic results in uncontrolled trials
III	Expert opinion based on clinical experience Descriptive studies Reports of expert committees

(pdhC1INH),<sup>31-33</sup> icatibant acetate,<sup>34-38</sup> ecallantide,<sup>39-41</sup> or recombinant human C1 inhibitor (rhC1INH).<sup>42-44</sup>

**2.2. STP or preprocedure prophylaxis.** STP or preprocedure prophylaxis consists of therapy before an invasive medical, surgical, or dental procedure or any other event that could trigger an edematous attack. Current available options include pdhC1INH, attenuated androgens (AAs), tranexamic acid (TA), and fresh frozen plasma (FFP).<sup>1,25,26</sup>

**2.3. LTP.** LTP is chronic therapy aimed at decreasing the frequency and severity of edematous attacks and might include antifibrinolytic agents, AAs, and even pdhC1INH.<sup>1,25,26,33</sup>

**A. AAs.** Danazol, stanozolol, and oxandrolone have been used. However, their use as maintenance treatment is accompanied by significant side effects.<sup>45-53</sup> Specific side effects in women include hyperandrogenemia with possible virilization (clitoromegaly); hirsutism; hoarseness or deepening of the voice; weight gain; menstrual irregularities<sup>54</sup>; pseudomenopause<sup>55,56</sup>; postmenopausal bleeding; burning, dryness, or itching of the vagina; and breast hypotrophy.<sup>50,57</sup>

Most adverse effects are dose related and can be minimized by titrating the AA dose to the lowest effective level (evidence level III).<sup>45,47,58-62</sup> However, AAs should be avoided in some patients because of secondary effects (evidence level III). Spironolactone, an androgen and aldosterone antagonist used as cotreatment of androgen-excess syndromes<sup>63,64</sup> and hirsutism,<sup>65</sup> could be used (100-200 mg/d) for controlling hirsutism in patients with HAE-C1-INH undergoing LTP with AAs (evidence level III). However, there are some concerns about the possibility of reducing the AA's efficacy (evidence level III).

Female patients taking AA prophylaxis can still ovulate and must be informed that conception is possible. Therefore women in their reproductive years should use additional contraceptive methods while undergoing AA LTP (evidence level III, see Section 5.3.1.3).

STP with AAs poses no specific problems for female patients. Virilization has not been observed in female patients with HAE-C1-INH who were given a short-course treatment with AAs for STP (up to 10 days).<sup>66,67</sup>

**B. Antifibrinolytics.** TA has been used as LTP with success,<sup>68</sup> although it is less effective than AAs.<sup>1,10</sup> TA can be given as LTP in female patients for whom AAs might be contraindicated and is the preferred treatment for LTP in prepubescent children.<sup>26,69</sup>

Adverse effects of antifibrinolytics have been reviewed.<sup>70</sup> Mild dysmenorrhea is the only specific secondary effect in female patients.<sup>12,71</sup>

In spite of hypothetical concerns about thrombus formation and thrombotic episodes related to the suppression of the fibrinolytic system,<sup>12</sup> the results of controlled clinical studies have not provided any evidence to support them.<sup>70,72</sup> However, patients with a personal or family medical history of thromboembolic disease might be at a greater risk of venous or arterial thrombosis, and an in-depth diagnostic workup might be necessary before initiating the use of TA (evidence level III).

**C. pdhC1INH.** Although some side effects have been described,<sup>1,32,33,73-76</sup> there is no known specific side effect that affects only female patients.

**D. FFP.** In countries in which pdhC1INH, icatibant, and ecallantide are not available, FFP, preferably virally inactivated, can be used.<sup>77,78</sup> Secondary effects have been reviewed.<sup>79</sup> No specific secondary effects in female patients have been shown.

**E. Bradykinin 2 receptor antagonist.** Icatibant acetate (Firazyr; Jerini AG, Berlin, Germany) is a synthetic selective bradykinin B2 receptor competitive antagonist that has been recently approved by the European Medicines Agency (July 2008) and authorized in several European countries for the treatment of acute HAE-C1-INH attacks in patients 18 years or older.<sup>80</sup> No specific secondary effects in female patients are known.<sup>38,81</sup>

**F. Kallikrein antagonist.** Ecallantide (DX-88 [Kalbitor]; Dyax Corp, Cambridge, Mass) is a new, potent, and specific plasma kallikrein inhibitor. It has been approved by the US Food and Drug Administration (December 2009) for the treatment of acute HAE-C1-INH attacks in patients 16 years or older. No specific secondary effects in female patients are known.<sup>82</sup>

**G. rhC1INH.** rhC1INH (Rhucin, Ruconest; Pharming NV, Leiden, The Netherlands) is produced in transgenic rabbits. It has been recently approved by the European Medicines Agency for the treatment of acute HAE-C1-INH attacks in patients 18 years or older (October 2010).<sup>83</sup> No specific secondary effects in female patients are known.

### 3. Diagnosis of HAE-C1-INH during pregnancy

An early and accurate diagnosis of HAE-C1-INH is important for both the mother and child. An HAE-C1-INH diagnosis can be reached by studying blood complement levels or by performing molecular genetic analysis of DNA obtained from cells.

**3.1. Diagnosis of HAE-C1-INH during pregnancy.** It is rare for HAE-C1-INH manifestations to present for the first time during pregnancy.<sup>84-86</sup> Serum C1-INH testing for the purpose of diagnosing HAE-C1-INH during pregnancy should be interpreted with caution because plasma C1-INH levels decrease during pregnancy in relation to the increase in plasma volume.<sup>87</sup> Transient low C1-INH levels with normalization after delivery have been found in pregnant women both with and without HAE-C1-INH.<sup>88,89</sup> Blood testing for C1-INH should be repeated postpartum to confirm the HAE-C1-INH diagnosis.

**3.2. Prenatal diagnosis.** See the "Genetic counseling" section.

**3.3. Preimplantation genetic diagnosis.** See the "Genetic counseling" section.

**3.4. Diagnosis of C1-INH deficiency in the newborn (postnatal diagnosis).** See the "Genetic counseling" section.

### 4. Genetic counseling

Genetic counseling, which should always be offered to patients and families with HAE-C1-INH, includes creating a pedigree

diagram, providing information on autosomal dominant inheritance, and identifying relatives who are at risk. In instances in which national laws and practice permit genetic testing and prenatal diagnosis or preimplantational genetic diagnosis, information on these procedures should be provided. HAE-C1-INH is a treatable disease with a highly variable phenotype, and prenatal diagnosis is therefore rarely requested.

**4.1. Inheritance.** The C1 inhibitor gene is the only gene known to cause HAE-C1-INH subtypes 1 and 2.<sup>1</sup> HAE-C1-INH is inherited in an autosomal dominant manner.<sup>1</sup> Penetrance is high; however, expressivity is highly variable. The severity of symptoms can be markedly different, even within families. There seems to be no clear genotype-phenotype correlation.<sup>1</sup> If a parent has HAE-C1-INH, the risk of passing the disease-causing mutation on to a child is 50%. If a child inherits a disease-causing mutation, the child will most likely have HAE-C1-INH at some time in his or her life (evidence of high penetrance); however, the severity of the disease cannot be predicted (evidence of variable phenotype).<sup>1</sup>

**4.2. Prenatal diagnosis in established pregnancy.** Prenatal diagnosis for hereditary angioedema in established pregnancy is only rarely requested. It can only be performed if the disease-causing mutation of the affected parent is known. Molecular genetic testing for the specific mutation is performed with cells from a chorion villus sample taken after the 10th week of gestation or from an amniotic fluid sample extracted after the 15th week of gestation. A chorion villus sample is preferable to amniotic fluid because sampling can be performed earlier in the pregnancy. The risk of an unintended abortion from either procedure performed by experienced professionals is approximately 0.5% to 1%.<sup>90</sup> In both cases a therapeutic abortion can be offered if the disease-causing mutation is discovered and if national laws and practices permit it.

**4.3. Prenatal diagnosis before established pregnancy: Preimplantation genetic diagnosis.** Preimplantation genetic diagnosis (PGD) might be more attractive than traditional prenatal diagnosis in families with HAE-C1-INH because it allows selection of embryos that are healthy with regard to HAE-C1-INH without interruption of an established pregnancy. PGD is a technique used for the diagnosis of genetic defects in embryos created through IVF before implantation and pregnancy. However, PGD is expensive and requires hormone therapy for the woman (see the "Fertility" section), and the pregnancy rate is low.<sup>91</sup> The first successful PGD of hereditary angioedema has recently been published.<sup>92</sup> Please see recommended procedures and prophylaxis below.

**Genetic testing.** Although genetic testing is not necessary in most patients to establish the diagnosis of HAE-C1-INH, it might aid in the diagnosis of cases in which biochemical measurements are inconclusive as it frequently occurs in newborns. It could also be helpful in the identification of family members at risk of HAE-C1-INH (presymptomatic testing). The disease-causing mutation of the particular family must be identified if prenatal diagnosis, PGD, or presymptomatic testing is requested. Tests should be performed by laboratories with experience in this type of analysis. The mutation responsible for C1-INH deficiency is only identified in 90% to 92% of patients with HAE-C1-INH.<sup>93,94</sup>

**4.4. Diagnosis of hereditary angioedema in neonates and infants.** The concentration of C1-INH in the umbilical blood of healthy neonates is approximately two thirds that of a normal adult.<sup>95</sup> The normal values of C1-INH and complement proteins show that age-dependent changes and concentrations

reach the levels for mature adults between 6 and 36 months for C1-INH and between 2 and 3 years of age for C4.<sup>96</sup> Because false-positive and false-negative HAE-C1-INH test results can occur in infants younger than 12 months, additional supplemental tests to confirm results should be performed at a later age.<sup>69,97</sup> Because biochemical tests bear inconclusive results in young children, genetic testing might be a safer and more direct way to determine whether a child has inherited HAE-C1-INH. However, it requires that the disease-causing mutation in the family is known. Genetic testing of newborns can be performed on blood from the umbilical cord or peripheral blood.

In general, genetic testing of asymptomatic children should only be performed in cases in which identification of genetic risks produces a specific benefit. HAE-C1-INH meets this prerequisite because presymptomatic testing in children at risk can help to ensure application of the correct treatment in the event of an attack.<sup>98,99</sup>

## 5. Management of pregnancy in patients with HAE-C1-INH

A prenatal diagnostics team should include specialists in ultrasound imaging, perinatology, gynecology, genetics, and HAE-C1-INH.<sup>1</sup>

**5.1. Influence of pregnancy, labor, delivery and breast-feeding in patients with HAE-C1-INH.** Pregnancy, labor, delivery, and breast-feeding affect HAE-C1-INH, and close monitoring is therefore recommended during these periods.

**5.1.1. Pregnancy.** Pregnancy can mitigate, aggravate, or have no effect on HAE-C1-INH edematous attacks. The frequency of attacks during previous pregnancies is not useful for predicting HAE-C1-INH events in later pregnancies.<sup>10,12,21,28,29,71,86,100-108</sup> Clinical symptoms are usually more severe during the first trimester.<sup>27-29,102</sup> Physiologic (neuroendocrine) changes associated with pregnancy (eg, nausea) and discontinuing maintenance treatment might affect how subjects rate their symptoms during the first trimester of pregnancy. In this trimester a woman's serum estrogen levels are higher than when not pregnant. The second trimester is the calmest period, possibly because of consistently high (and proportional) hormone levels. In the third trimester, already high progesterone levels increase and reach a plateau. At the same time, increases in the concentrations of estrogens and placental prolactogenic hormones are associated with more frequent edema attacks. This contrasts with the fact that women for whom menstruation was found to have provoked attacks earlier had fewer symptoms in the third trimester.<sup>29</sup>

Onset of symptoms of HAE-INH early in life is associated with more frequent and more severe attacks during pregnancy.<sup>29,105</sup>

Carrying a fetus with HAE-C1-INH can cause the number of edema events for a pregnant woman to increase. This finding raises the possibility that the C1-INH protein in the fetus is "shared" with the mother through placental or fetal circulation.<sup>29</sup>

The location of attacks remains the same as in the prepregnant state, except that abdominal attacks occur more frequently during pregnancy.<sup>29,86</sup> and might make it more difficult to perform a differential diagnosis with other complications associated with pregnancy.<sup>27,29,86,101,109</sup> When an abdominal ultrasound detects free peritoneal fluid and edema of the intestinal wall, thereby suggesting an edema event, confirmation can take the form of clinical improvement 30 to 60 minutes after the administration of pdhC1INH and a follow-up ultrasound with normal results.<sup>29</sup>



**TABLE II.** Available drugs for treatment of patients with HAE-C1-INH

Drug	Trade name	Company	Drug description
pdhC1INH	Beriner	CSL-Behring, Marburg, Germany	Human plasma-derived C1 esterase inhibitor
Human plasma-derived nanofiltered C1-INH	Cinryze	Viropharma, Exton, Pa	Human plasma-derived C1 esterase inhibitor
rhC1INH produced in transgenic rabbits	Rhucin/Ruconest*	Pharming NV, Leiden, The Netherlands	Recombinant human inhibitor of C1-esterase (produced in transgenic rabbits)
FFP		Several	Plasma derivative
Icatibant acetate	Firazyr	Jerini AG/ Shire, Berlin, Germany	Synthetic peptide (10 amino acids)
Ecallantide	Kalbitor	Dyax Corp, Cambridge, Mass	Synthetic protein (60 amino acids)
TA	Amchafibrin, Cyklokapron	Pfizer, New York, NY	Antifibrinolytic
Danazol	Danatrol, Danocrine, Danol	Sanofi-Aventis, Paris, France	AA (17- $\alpha$ -alkylated androgens)
Stanozolol	Winstrol	Winthrop, Barcelona, Spain	AA (17- $\alpha$ -alkylated androgens)
Oxandrolone	Oxandrin	Savient Pharmaceuticals, East Brunswick, NJ	Attenuated androgen (17- $\alpha$ -alkylated androgens)

AA, Attenuated androgen; EMA, European Medicines Agency; FDA, US Food and Drug Administration; EU, European Union; US, United States.

\*Conestat alfa will be marketed as Ruconest in Europe and Rhucin in other parts of the world.

**5.1.2. Labor and delivery.** Although both labor and delivery involve substantial mechanical trauma, only rarely do they provoke an edematous attack. Such attacks can occur immediately after or within 48 hours of delivery. After childbirth, the prevalence of localized swelling of the vulva exceeds that of genital edema experienced before pregnancy.<sup>27,29,86,102,104,105,108-110</sup>

A number of case series report a higher frequency of edema attacks in the puerperium.<sup>85,111,112</sup> A case in which a mother died after experiencing perineal swelling after delivery was clearly associated with septic shock rather than C1-INH deficiency.<sup>113</sup>

Eighty percent to 90% of births are spontaneous vaginal deliveries. The rate of cesarean section is not higher than in the general population.<sup>27,29,108</sup>

**5.2. Spontaneous abortion and premature labor.** It has been suggested that symptomatic patients with HAE-C1-INH have a higher rate of spontaneous abortion and premature labor when compared with their healthy relatives<sup>22</sup> because bradykinin causes the smooth muscles in the uterus to contract, as seen in a study with rats.<sup>114</sup> However, other studies have not found an increase in the number of spontaneous abortions<sup>29,108</sup> or premature births.<sup>29</sup>

**5.3. Treatment of HAE-C1-INH during pregnancy.** In general, the medication dosage for women is the same regardless of whether they are pregnant. However, therapeutic options might be limited, and patients should be managed on an individual basis.

**5.3.1. LTP.** Patients with a history of miscarriages, high-risk pregnancies, or frequently recurring severe attacks might require LTP.

**5.3.1.1. pdhC1INH.** pdhC1INH appears to be safe and effective during pregnancy and lactation for either prophylaxis or acute therapy,<sup>28,29,115-117</sup> although no controlled studies with pregnant women have been conducted.

**5.3.1.2. Antifibrinolytics.** LTP with TA during pregnancy is considered medically indicated only when pdhC1INH is unavailable (evidence level III).

TA crosses the placenta, but no mutagenic activity or harmful fetal effects of TA have been reported,<sup>70</sup> and reproduction studies in animals have shown no teratogenic effects.<sup>118,119</sup> However, studies of the teratogenic risk in human subjects have not yet been performed. Doses of TA, similar to those of patients with HAE-C1-INH, have been administered during pregnancy for other diseases but for a much shorter period of time. Treatment is usually administered during the second half of pregnancy. It is well tolerated and does not have a negative effect on the delivery of healthy children.<sup>120</sup> Given the lack of data on the use of TA throughout entire pregnancies, its potential risks and benefits must be considered carefully.

**5.3.1.3. AAs.** AAs are contraindicated for use during pregnancy, particularly during the first trimester. AAs cross the placenta and can affect fetal development by enhancing male secondary sexual characteristics in the female fetus.<sup>61,121-123</sup> Exposure to testosterone during pregnancy might cause placental insufficiency by decreasing the expression and functioning of system A transporters, which can contribute to fetal growth retardation.<sup>124</sup> No animal experiments or *in vitro* mutagenicity studies have been performed.

TABLE II. (Continued)

Mechanism of action	Administration route	Indication	FDA approval status	EU approval status
C1-INH replacement	Intravenous	Acute treatment STP LTP	Approved by FDA for acute treatment	Approved by EMA for acute treatment and self-administration
C1-INH replacement	Intravenous	Acute treatment STP LTP	Approved by FDA for LTP	Approved by EMA for acute treatment, STP, LTP
C1-INH replacement	Intravenous	Acute treatment		Approved by EMA for acute treatment
C1-INH replacement	Intravenous	STP Acute treatment	Available in US	Available in EU
Blockage of B2R	Subcutaneous	Acute treatment	Approved by FDA for acute treatment and self-administration	Approved by EMA for acute treatment and self-administration
Selective inhibitor of plasma kallikrein	Subcutaneous	Acute treatment	Approved by FDA for acute treatment	
Inhibition of fibrinolysis	Oral, intravenous	LTP STP	Available in US	Available in EU
Increase in plasma C1-INH levels	Oral	LTP STP	Available in US	Available in EU
Increase in plasma C1-INH levels	Oral	LTP STP	Available in US, not approved for their use in HAE-C1-INH (off-label use)	Available in a few countries of the EU but not approved for their use in patients with HAE-C1-INH (off-label use)
Increase in plasma C1-INH levels	Oral	LTP	Available in US	Not available

5.3.1.4. Virally inactivated FFP. If pdhC1INH is not available and antifibrinolytics are contraindicated or ineffective, virally inactivated fresh frozen plasma (viFFP) might serve as an alternative for LTP (evidence level III).<sup>77,125</sup> Limited data exist on the long-term use of FFP during pregnancy.

5.3.2. STP. The treatment of choice is pdhC1INH.<sup>26</sup> If this is not available, viFFP can be administered.<sup>126</sup>

5.3.2.1. Amniocentesis/chorial biopsy. No references were found, but STP with pdhC1INH is recommended (evidence level III).

5.3.2.2. Surgical artificial abortion. STP with pdhC1INH is recommended (evidence level III). viFFP can be used if pdhC1INH is not available. Alternatively, medications for acute treatment should be readily available.<sup>29</sup>

5.3.2.3. Medical artificial abortion. The only reference to medical abortion in patients with HAE-C1-INH has cited the administration of 600 mg of mifepristone and gemeprost pessary insertion.<sup>127</sup> The need for STP in this setting has not been established, but acute treatment should be readily available.

5.3.2.4. Delivery and puerperium. Patients with HAE-C1-INH should be delivered in hospitals that provide quick access to consultants in obstetrics, anesthesiology, perinatology, and HAE-C1-INH. Routine prophylaxis before uncomplicated natural deliveries is not recommended, but pdhC1INH should be readily available (evidence level III). A physician familiar with HAE-C1-INH management should be available for consultation by telephone, if not in person. STP is recommended before

labor and delivery when HAE-C1-INH is severe, symptoms have recurred frequently during the third trimester of pregnancy, or the patient's medical history includes genital edema caused by mechanical trauma (evidence level III). Administration of pdhC1INH is recommended if forceps delivery or vacuum extraction is performed. After vaginal delivery, patients with marked perineal swelling or other postpartum complications should be considered at higher risk for acute attacks, closely monitored for 72 hours after delivery, and treated with pdhC1INH when necessary.<sup>85,108,112,113,128</sup>

5.3.2.5. Cesarean section (abdominal delivery). A cesarean section performed after achievement of general anesthesia might trigger an edema attack because of the aggregate effect of endotracheal intubation, surgical stress, and tissue damage resulting from the surgical incision. Epidural anesthesia is recommended for cesarean sections to avoid endotracheal trauma and local airway edema (evidence level III). STP is recommended with pdhC1INH (evidence level III).<sup>25,110,129,130</sup> Emergency procedures should not be delayed if pdhC1INH is not immediately available because pdhC1INH can be administered at a later time.

### 5.3.3. Acute therapy.

5.3.3.1. pdhC1INH. pdhC1INH is recommended as the first-line therapy in pregnancy (evidence level III).<sup>28,29,117</sup> Side effects are rare.

5.3.3.2. viFFP. If pdhC1INH is not available, viFFP can be administered for HAE-C1-INH attacks. Risks and precautions are similar to those in nonpregnant women.<sup>21,26,107,109,129</sup> One case of

anaphylaxis has been reported with FFP administered for an acute HAE-C1-INH attack.<sup>107</sup>

However, there is a possible risk of worsening HAE symptoms because in addition to C1-INH viFPF also supplies substrates (Factor XII, prekallikrein, and high molecular weight kininogen), which can produce an increase in bradykinin before the supplied C1-INH has had time to act.<sup>77-79</sup> Physicians must be prepared for such a situation.

**5.3.3.3. Antifibrinolytics.** Antifibrinolytics have been administered during pregnancy, but pdhC1INH is usually more efficacious. Antifibrinolytics can be administered for mild edema attacks.<sup>101</sup>

**5.3.3.4. Bradykinin 2 receptor antagonist (icatibant acetate).** No data are available for use during pregnancy or lactation.<sup>81</sup>

**5.3.3.5. Kallikrein antagonist (ecallantide).** No data are available for use during pregnancy or lactation.<sup>82</sup>

**5.3.3.6. rhC1INH.** No data are available for use during pregnancy or lactation.

**5.4. Postpartum follow-up.** Close follow-up by staff familiar with HAE-C1-INH is recommended for at least 72 hours after delivery (evidence level III). Before the patient has been sent home, she should be informed about the increased risk of postpartum swelling and provided with a treatment plan.

**5.5. Home care.** The considerations and recommendations for home care are the same as for care in nonpregnant female patients.<sup>26,131</sup>

**5.6. Family planning.** Genetic counseling should be given to any patients with HAE-C1-INH of childbearing age (see the "Genetic counseling" section).

**5.6.1. LTP.** Between 30% and 40% of patients with HAE-C1-INH take some form of LTP,<sup>10,62,132</sup> which might affect fertility or pregnancy and fetal development. Effects on fertility and possible teratogenic effects of LTP and other therapies should be explained to and understood by patients.

**5.6.1.1. Antifibrinolytic agents.** TA should be stopped before attempting conception, when possible. It is eliminated by rapid renal clearance (half-life of 2-8 hours).<sup>133,134</sup> Suspending TA several days before attempting conception should suffice (evidence level III).

**5.6.1.2. AAs.** The mean half-life for danazol was  $9.44 \pm 2.74$  hours.<sup>135</sup> It is recommended that AAs be discontinued 2 months before attempting conception (evidence level III). A number of physicians contend that the half-life of danazol would require a much shorter period for avoiding AAs before attempting conception. A negative pregnancy test result should be obtained before commencing AA therapy. If a patient becomes pregnant while taking AAs, administration of the drug should be discontinued and the family should be informed of the risk of abnormalities of sexual differentiation in the fetus.

**5.6.1.3. pdhC1INH.** Treatment with pdhC1INH concentrate might continue during the period of conception, pregnancy, and delivery (evidence level III).<sup>27-29,86,127</sup>

**5.6.1.4. Ecallantide, icatibant acetate, and rhC1INH.** There are no data on use during pregnancy, and these drugs should therefore be avoided before attempting conception. Their half-lives are short (ecallantide,  $2.0 \pm 0.5$  hours<sup>136</sup>; icatibant acetate, 1-2 hours<sup>34</sup>; and rhC1INH, 3 hours<sup>43</sup>). Patients should stop taking them 1 week before attempting conception (evidence level III).

## 6. Management of lactation in patients with HAE-C1-INH

Lactation might be associated with an increased number of edematous attacks,<sup>27</sup> particularly in women with predominantly abdominal symptoms.<sup>29</sup> A relationship between prolactin levels and the number of abdominal attacks has been shown.<sup>137</sup> Thus the transient increase in the frequency of attacks during the postpartum period might be induced by increased levels of serum prolactin.<sup>135</sup> Ceasing lactation itself might reduce attack frequency by causing a decrease in serum prolactin levels.<sup>138</sup>

pdhC1INH is the treatment of choice for LTP, STP, or acute treatment during lactation (evidence level III).

When TA is excreted into breast milk, its concentration level is approximately 1% of the concentration of TA in maternal serum.<sup>139</sup> It is therefore not recommended for administration during breast-feeding.

It is not known whether anabolic steroids are excreted into breast milk. Because of their potential side effects in children, it is recommended that the mother cease breast-feeding before commencing AA therapy.

## 7. Contraception

### 7.1. Oral contraceptive pills containing estrogen.

Between 60% and 80% of women with HAE-C1-INH who use oral contraceptive pills containing estrogen have had an increase in both the frequency and severity of attacks.<sup>18,19,108,140</sup>

Animal studies have shown that 17  $\beta$ -estradiol favors the increase of Factor XII, kallikrein, and kinin concentrations. In addition, estrogens regulate B2 receptor gene expression and function. In healthy women taking oral contraceptives, Factor XII, prekallikrein, kallikrein, and kinin levels increase, and C1-INH levels decrease.<sup>141-147</sup>

### 7.2. Combined parenteral estrogen-progestin (patch and vaginal ring).

Combined parenteral estrogen-progestin (patch and vaginal ring) contains as much ethinyl estradiol as oral contraceptives and has similar hepatic side effects. Experience with HAE-C1-INH is limited. A single patient with HAE-C1-INH using a combined transdermal contraceptive was reported to exhibit good tolerance after 26 months of use.<sup>148</sup> However, another patient experienced her first HAE-C1-INH event while using the contraceptive patch (A. Gompel, personal data). There is no reason to believe that contraceptive patches and vaginal rings are tolerated any better than oral contraceptives.

### 7.3. Progestins (synthetic progestogens that have progestinic effects similar to progesterone): Evidence level III.

Progesterone-only pills (POPs) are widely used. POPs led to improvement in 64.3% of women with HAE-C1-INH.<sup>108</sup> Other studies reported that 5 of 8 patients with HAE-C1-INH who were taking pills containing norgestrienone experienced reduced HAE-C1-INH symptoms.<sup>149-151</sup> In one case the C1-INH antigen level increased.<sup>149</sup> POPs use normethyltestosterone derivatives at low doses and are therefore considered mild androgens. However, they can exert a partial antigonadotropic effect in some patients. Control of a woman's cycle can vary depending on the woman's response to the secretion of follicle-stimulating hormone and luteinizing hormone. The gynecologic tolerance is often poor, with breakthrough bleeding, pelvic discomfort, and mastalgia. Because functional cysts can occur in about 30% of cycles, these contraceptives can produce hyperestrogenemia, which

might explain the partial tolerance in some women with HAE-C1-INH. However, in two thirds of patients with HAE-C1-INH, they are well tolerated and can be recommended.

Etonogestrel, the active metabolite of the inactive prodrug desogestrel, is another contraceptive alternative that can be used as an implant (Implanon or Nexplanon; MSD, Whitehouse Station, NJ) or as a contraceptive vaginal ring (Nuvaring, MSD). Implanon has been well tolerated by some patients with HAE-C1-INH (J. Gooi, personal data).

#### 7.4. Progestin in high doses: Evidence level III.

**Normethyltestosterone derivatives.** Normethyltestosterone derivatives have not been systematically evaluated in patients with HAE-C1-INH but are commercialized in a number of European countries. Some of the normethyltestosterone derivatives are norethisterone derivatives (norethisterone, norethisterone acetate, lynestrenol, and ethynodiol diacetate). They are usually administered in a single daily dose of 10 mg. At this dosage level, they are potent antigonadotropic agents with mild androgenic activity. They can display metabolic and vascular side effects related to their androgenic potencies. However, these side effects might be less important than those observed with the use of danazol. Lynestrenol has been used with good tolerance and has decreased the frequency of attacks in some women and even permitted some women to stop taking danazol (A. Gompel, personal data). However, it is difficult to recommend their combined use with danazol because of the possible side effects. Likewise, it is difficult to recommend their use in combination with TA because of a potentially greater risk of vein thrombosis.<sup>152</sup> Tibolone is a normethyltestosterone derivative developed for climacteric symptoms and osteoporosis in postmenopausal women. It has been used in 8 premenopausal and postmenopausal women with HAE-C1-INH subtype I, with good clinical results.<sup>153</sup> However, there is no information on the contraceptive effects of this compound in premenopausal women.

**Pregnanes and norpregnanes.** In many countries medroxyprogesterone acetate (MPA) is the only alternative available to women who exhibit intolerance or low compliance to POPs and for whom a combined pill is contraindicated. We have found no reports on depot MPA in women with HAE-C1-INH, but in theory, it can be used. Depot MPA has limited cycle tolerance and glucocorticoid and androgenic potencies, which might limit its clinical tolerance.

Other progestins have not been developed as contraceptive agents but are used for therapeutic purposes. Because of their antigonadotropic properties, they have been used in France for more than 20 years, mainly as a contraceptive for women who have a thrombotic risk contraindication to combined oral contraceptive pills.<sup>154-156</sup>

Chlormadinone acetate is the most widely used and has good antigonadotropic efficiency.<sup>157,158</sup> It has been used in a series of women with HAE-C1-INH with satisfactory results (A. Gompel, personal data).

Nomegestrol acetate is a norpregnane derivative with strong antigonadotropic activity and has shown positive results in women who have HAE-C1-INH (A. Gompel, personal data).

Cyproterone acetate is a very strong antigonadotropic pregnane progestin that has potent antiandrogenic properties and has been reported to worsen HAE-C1-INH. It therefore cannot be recommended for women with HAE-C1-INH.<sup>159</sup>

**7.5. Intrauterine device: Evidence level III.** Intrauterine devices (IUDs) were well tolerated by 83.3% of patients with HAE-

C1-INH.<sup>108</sup> Insertion is generally well tolerated without HAE-C1-INH prophylaxis before insertion. However, acute HAE-C1-INH treatment (pdhC1INH concentrate, icatibant acetate, ecallantide, or rhC1INH) should be readily available at the time of insertion.

The progesterone-eluting IUD (Mirena) could be beneficial for patients with HAE-C1-INH (T. Caballero, personal data), whereas the estrogen-eluting IUD could worsen HAE-C1-INH symptoms.

#### 7.6. Emergency postcoital contraception

**7.6.1. Emergency contraceptive pill (the morning-after pill).**

**7.6.1.1. Progestin-only emergency contraceptive pill.** The progestin-only emergency contraceptive pill is available and has been shown to be well tolerated by some patients with HAE-C1-INH (T. Caballero, personal data; evidence level III).

**7.6.1.2. Estrogen and combined emergency contraceptive pill.** The estrogen and combined emergency contraceptive pill can worsen HAE-C1-INH (evidence level III).

**7.6.2. IUD insertion.** The copper-T IUD can be used up to 5 days after unprotected intercourse to prevent pregnancy and has been well tolerated by a woman with HAE-C1-INH.<sup>160</sup>

**7.7. Principle barrier methods of contraception.** Principle barrier methods of contraception (eg, condoms or contraceptive foams) have not been associated with any problems.

**Contraception recommendations.** Contraceptives containing estrogen should be avoided (evidence level III). Barrier methods, IUDs, POPs, and progestins can be used.

### 8. Menstruation

Puberty worsened the severity and frequency of HAE-C1-INH events in 56.7% of cases (evidence level III).<sup>108</sup>

Most reports revealed that menses can precipitate acute episodes (evidence level III). In PREHAEAT studies menses and ovulation provoked attacks in 35.3% and 14% of cases, respectively (evidence level III).<sup>108</sup> Diagnosis of abdominal angioedema during menses is very difficult. The main differential diagnosis is pelvic endometriosis, which might be suggested if dyspareunia is a coexisting condition. Clinical examination by experienced professionals is recommended, and pelvic ultrasonography or magnetic resonance imaging might also be considered. The diagnosis of abdominal edema is likely when severe abdominal pain is present (visual analog scale score >5) or there are either ascites or intestinal edema and where improvement follows specific treatment for HAE-C1-INH (icatibant acetate, pdhC1INH concentrate, ecallantide, or rhC1INH; evidence level III).

### 9. Menopause

The PREHAEAT study reported that menopause improved HAE-C1-INH in 13% of patients and worsened it in 32% (evidence level III).<sup>108</sup>

Estrogen replacement therapy must not be used for menopause (evidence level III). The case of a menopausal patient with HAE-C1-INH who had her first HAE-C1-INH attack after beginning estrogen replacement therapy for menopause has been reported.<sup>161</sup> The relationship between the worsening of HAE-C1-INH symptoms and estrogen replacement therapy can be explained by the decrease in the activity of the angiotensin-converting enzyme, which is involved in bradykinin catabolism, in addition to the effects of estrogens on bradykinin pathways with an increase in Factor XII, prekallikrein, and bradykinin values.<sup>162-166</sup>



The use of phytoestrogens as an alternative treatment for hot flushes during menopause has not been evaluated for women with HAE-C1-INH. However, they clearly cannot be recommended because of their estrogenic potencies (evidence level III).

Progesterone and progestins can alleviate hot flushes and can be offered to women who have HAE-C1-INH.<sup>167,168</sup> Tibolone, a normethyltestosterone derivative used in symptomatic postmenopausal women, can also be used but should be given in place of rather than in combination with danazol because of a risk of greater side-effects because of their common properties.<sup>153</sup>

Nonhormonal alternatives, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and clonidine can be used for resistant hot flushes and insomnia.<sup>169</sup>

As for selective estrogen receptor modulators, there are no reports about the use of raloxifene in patients with HAE-C1-INH, but a report on tamoxifen as an adjuvant breast cancer therapy described a worsening of HAE-C1-INH symptoms.<sup>170</sup>

No studies have been published on the treatment of osteoporosis with bisphosphonates or strontium ranelate in patients with HAE-C1-INH, but there is no apparent contraindication.

## 10. Polycystic ovary syndrome

A study of pelvic ultrasound scans performed in 13 patients with HAE-C1-INH reported an increased frequency of polycystic ovary syndrome and multifollicular ovaries, with rates of 38.4% and 53.8%, respectively.<sup>171,172</sup> However, the PREHAEAT study did not reveal a higher frequency of polycystic ovary syndrome in the HAE-C1-INH population. The rate was found to be 4.7% compared with 5% to 10% in the general population in Europe (evidence level III).<sup>108</sup>

## 11. Gynecologic surgery

STP should be performed with the same drugs and dosages as in other patients with HAE-C1-INH.<sup>26</sup>

## 12. Breast cancer

Microsomal cytochrome P450 enzyme aromatase (CYP 19) can convert some androgens into estrogens. There is no evidence that danazol or stanozolol can be aromatized. Preclinical studies reported no effect or reduced aromatase activity or levels in the endometrium or endometriotic lesions with danazol therapy.<sup>173-175</sup> However, conflicting data on androgen's effects in patients with breast cancer suggests danazol should not be a first-line therapy for patients who have both HAE-C1-INH and breast cancer. If no alternative HAE-C1-INH therapy is available to control HAE-C1-INH attacks, then the oncologist and the HAE-C1-INH therapist should discuss whether to use danazol.

**Tamoxifen.** Some HAE-C1-INH experts express concern about the influence of antiestrogens, which have some agonistic effects on estrogen receptors, especially on the liver. Worsening of HAE-C1-INH and lower C1-INH levels were confirmed in a recent publication.<sup>170</sup>

## 13. Endometrial cancer

In the majority of cases, endometrial cancer is estrogen dependent. Progestogens and androgens are not contraindicated, and danazol can be used.

## 14. Cervical cancer

Cervical squamous cell cancer is not hormone dependent, and there is no contraindication to AA HAE-C1-INH prophylaxis.

Cervical adenocarcinoma might be estrogen dependent, and the use of AAs is not contraindicated.<sup>176</sup>

## 15. Infertility

AAs were reported to reduce fertility in male patients with HAE-C1-INH. Sexual dysfunction and temporary infertility (reversible oligospermia and testicular atrophy) might ensue after the prolonged administration or treatment with high doses of AAs.<sup>177-179</sup> Male patients with HAE-C1-INH who have fertility problems and wish to father children should be warned to avoid androgens. However, there are no data about the possible influence of AAs or other HAE-C1-INH medications on fertility in female patients with HAE-C1-INH. Nevertheless, a multicenter study in Europe revealed that the fertility rate of female patients with HAE-C1-INH was reported to be the same as for the general population.<sup>108</sup>

Antifibrinolytics have no effect on the motility of spermatozoa and do not impair fertility.

Fertility studies and fertilization techniques can be difficult to manage in female patients with HAE-C1-INH.

**Salpingography.** Prophylaxis with pdhC1INH is recommended (AAs, antifibrinolytics, or viFFP when pdhC1INH is not available; evidence level III).

**Intrauterine insemination.** There is a risk of increased frequency and severity of angioedema attacks caused by higher levels of endogenous estrogens as a result of treatment with injectable gonadotropins (usually follicle-stimulating hormone analogues) to induce ovarian stimulation.<sup>180</sup> If intrauterine insemination (also called artificial insemination) is indicated, ovarian stimulation should be closely monitored. In cases of hyperstimulation or high levels of estrogens, prophylaxis with pdhC1INH should be used (evidence level III).

**IVF.** IVF in female patients with HAE-C1-INH could be associated with an increase in the frequency and severity of angioedema attacks because of a rapid increase in endogenous estrogens induced by injectable gonadotropins used for ovarian stimulation. If IVF is indicated, it should be performed as often as possible during spontaneous cycles when estradiol is less likely to reach high levels and the risk of hyperstimulation is lower. IVF should be attempted after procedures that help decrease the risk of hyperstimulation syndrome.<sup>181,182</sup> pdhC1INH prophylaxis should be used before aspiration for oocyte retrieval (evidence level III). There are no data on the treatment or prophylaxis of attacks during severe hyperstimulation after ovarian induction. This syndrome is associated with severe hypovolemia, ascites, and an increased risk of thrombosis.<sup>183,184</sup> Antifibrinolytics should be avoided, and in the event of an attack, pdhC1INH should be used. Another approach could be intermittent prophylaxis with pdhC1INH (evidence level III).

Although no evidence exists of an increased prevalence of premature ovarian failure in women with HAE-C1-INH, they are susceptible to this condition. In the case of an oocyte donation, estradiol and progesterone are administered before and after embryo transfer to physiologic levels. The risk of an HAE-C1-INH attack might be similar to of the risk during pregnancy (see the "Pregnancy" section).

In summary, this consensus seeks to further assist clinicians in the management of female patients with hereditary angioedema.

The final version has been read and approved by all authors.

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