Treating HAE during pregnancy

- Sarah is a 30-year-old female that has HAE and wishes to conceive
- She attends an angioedema specialist centre for guidance on management and treatment of HAE throughout her pregnancy journey
- The following case is based on experiences from real patient cases, and content and images have been adapted for educational purposes

*Images may not represent real patients

Case created by:

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Patient history I

- At the age of 21, Sarah was diagnosed with HAE type I, having experienced recurrent episodes of abdominal pain since the age of 9
  - C1-esterase inhibitor (C1-INH) activity level of 0.24 U/mL
  - Sarah also experienced peripheral swellings prior to her diagnosis, for which she had never sought medical attention
- Due to high disease burden with frequent abdominal attacks and frequent absenteeism, Sarah received routine prophylactic treatment with intravenous C1-INH concentrate twice weekly

1. Studies suggest the average delay in HAE diagnosis is 8.5 years

A. True

B. False

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B. False

Feedback

- The current understanding of HAE has greatly improved in recent decades, leading to growing awareness, improved management, and better outcomes[1]
- The average delay in HAE diagnosis from the initial presentation of symptoms is 8.5 years[2]
  - Nevertheless, some studies report diagnostic delays in excess of 13–20 years[1]
- These delays can be worrisome given the significant risk of life-threatening laryngeal angioedema in affected individuals[1]
  - One recent study identified a significantly higher mortality by asphyxiation in undiagnosed HAE patients[3]

1. Henao *et al. Ther Clin Risk Manag*. 2016;12:701–711. 2. Zanichelli et al. Allergy Asthma Clin Immunol. 2013;9(1):29. 3. Bork *et al. J Allergy Clin Immunol*. 2012;130(3):692–697.

Patient history II

- At the age of 27, Sarah continued to experience frequent abdominal attacks, despite routine prophylaxis with intravenous C1-INH concentrate
- Sarah and her partner decided they wanted to conceive; however, at the age of 29 she was diagnosed with subfertility
- She was prescribed an estrogen receptor modulator, clomifene citrate, to increase the chance of a successful pregnancy

C1-INH, C1-esterase inhibitor

Sarah’s concerns regarding in vitro fertilization (IVF) and pregnancy

- Upon treatment with clomifene citrate, Sarah experienced an increase in attacks and continued emotional distress
- One year later, IVF treatment was recommended by her gynecologist
- Sarah admits she was anxious about several factors regarding the management of her HAE throughout IVF and pregnancy:
  - Venous access
  - Sick leave
  - Anxiety of inheritance
  - Fear of deterioration
  - Fear that attacks would harm her child

2. Which factors may cause an increase in angioedema attack frequency during IVF therapy?

A. Emotional distress

B. Stimulation of ovulation

C. Increased estrogen levels

D. All of the above

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Feedback

- In addition to specific medical procedures, there can be patient-specific angioedema-inducing situations such as emotional stressors that can precipitate attacks[1]
- Various factors unique to women, including menses, ovulation, hormonal contraception, pregnancy, childbirth, breastfeeding, and menopause, lead to fluctuations in estrogen, which can influence HAE attack frequency and severity[2–4]
  - In a survey of women with HAE (n = 150), 35% reported that attacks were triggered by menstruation and 14% by ovulation[5]
  - Another study by Bork *et al.* reported that menstruation and ovulation may trigger skin swelling and abdominal pain[6]
- Increased estrogen levels can worsen the disease course of HAE and can present problems for managing contraception, IVF and menopause in women[7]
  - It has been reported that increased concentration of estrogens and placental prolactogenic hormones are associated with more frequent edema attacks

1. Maurer *et al. Allergy*. 2022. 2. Levy *et al. Allergy Asthma Clin Immunol*. 2020;16;8. 3. Bouillet *et al. Am J Obstet Gynecol*. 2008;199(5):484.
4. Zotter *et al. Orphanet J Rare Dis*. 2014;28:9:44. 5. Banerji *et al. Womens Health (Lond)*. 2016;12(3):351–361. 6. Bork *et al. Am J Med*. 2006;119(3):267–274.
7. Caballero *et al. J Allergy Clin Immunol*. 2012;129(2):308–320.

3. Which treatment strategy would you recommend for Sarah? (select all that apply)

A. Optimize dosing strategy of intravenous C1-INH concentrate

B. Consider another route of administration for C1-INH concentrate

C. Refer to a psychologist with HAE expertise

D. Recommend that the patient does not have children

C1-INH, C1-esterase inhibitor

3. Which treatment strategy would you recommend for Sarah? (select all that apply)

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C1-INH, C1-esterase inhibitor

Feedback

- Recent World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines state that plasma-derived C1-INH (pdC1-INH) is recommended as first-line therapy (short-term prophylaxis [STP], long-term prophylaxis [LTP] and on-demand treatment) for pregnant or breast-feeding patients with HAE type I or II, as it is safe and effective[1]*
- The subcutaneous formulation of pdC1-INH may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1-INH compared to LTP with intravenous C1-INH, allowing for better symptom control[1]
- Psychologists can work together with physicians to turn the lack of certainty in patient awareness and ability to identify strategies for flexible management of HAE[2]

1. Maurer *et al. Allergy*. 2022. 2. Savarese *et al. Orphanet J Rare Dis*. 2021;16(1):23.

**Approved product indications vary worldwide*

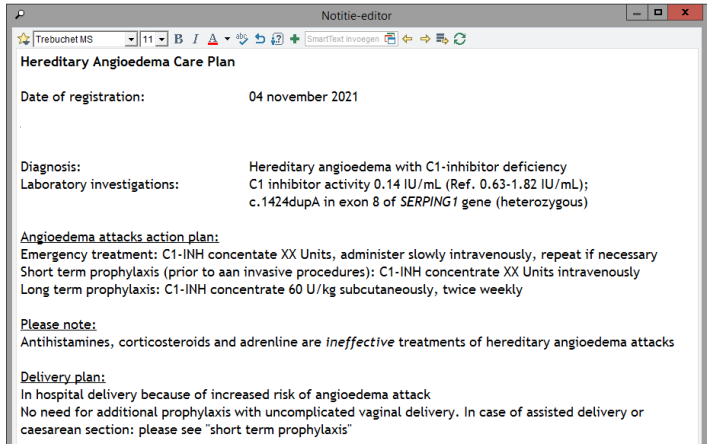
Next course of action

- Sarah's intravenous C1-INH prophylaxis dosing regimen was optimized in an effort to provide improved attack prevention
- During the Coronavirus 2019 pandemic, Sarah's IVF procedure was postponed
- She continued to have frequent angioedema attacks despite having increased the frequency of infusions of intravenous C1-INH concentrate
  - At her last visit, she presented with an angioedema control test (AECT) score of 7, which represented poor disease control
- Sarah was then prescribed subcutaneous C1-INH concentrate, with the aim of achieving better disease control through improved steady-state plasma concentrations of C1-INH and through the reduced treatment burden offered by subcutaneous administration

C1-INH, C1-esterase inhibitor; IVF, in-vitro fertilization

At today's appointment…

- At her current appointment, after 3 months of prophylactic treatment with subcutaneous C1-INH, Sarah has only experienced 2 mild attacks
  - She has an improved AECT score of 14
- Sarah has gained confidence in her HAE treatment and overall disease control, and has now planned her IVF treatment in the near future
  - She has visited you today to discuss what to expect during the course of her planned pregnancy and to create a personalized treatment and management plan for her HAE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Hereditary Angioedema Care Plan

Date of registration: 04 november 2021

Diagnosis: Hereditary angioedema with C1-inhibitor deficiency
Laboratory investigations: C1 inhibitor activity 0.14 IU/mL (Ref. 0.63-1.82 IU/mL);
c.1424dupA in exon 8 of *SERPING1* gene (heterozygous)

Angioedema attacks action plan:
Emergency treatment: C1-INH concentate XX Units, administer slowly intravenously, repeat if necessary
Short term prophylaxis (prior to aan invasive procedures): C1-INH concentrate XX Units intravenously
Long term prophylaxis: C1-INH concentrate 60 U/kg subcutaneously, twice weekly

Please note:
Antihistamines, corticosteroids and adrenline are *ineffective* treatments of hereditary angioedema attacks

Delivery plan:
In hospital delivery because of increased risk of angioedema attack
No need for additional prophylaxis with uncomplicated vaginal delivery. In case of assisted delivery or caesarean section: please see "short term prophylaxis"

AECT, Angioedema Control Test; C1-INH, C1-esterase inhibitor

4. HAE disease activity always deteriorates during pregnancy

A. True

B. False

4. HAE disease activity always deteriorates during pregnancy

A. True

B. False

Feedback

- Pregnancy can mitigate or aggravate HAE disease activity or have no effect
- Several conditions and events are known to trigger HAE attacks in pregnant patients. Guidelines suggest that the anatomical, physiological, and hormonal changes during pregnancy may influence the manifestations and affect the course and treatment of HAE type I and type II[1–3]
  - The increase in estrogens during pregnancy may be a trigger for HAE attacks and attack frequency often increases during pregancy[1, 4]
  - Pregnant patients with HAE type I or type II require vigilant care and meticulous monitoring by their HAE specialist. All patients with HAE should be educated about triggers that may induce attacks[1]
  - Attack frequency during previous pregnancies is not predictive for later pregnancies
- The management of pregnancy in patients with HAE is often a clinical challenge owing to potential worsening of the disease in relation to the physiological increase in estrogens and the limited treatment options[2]
- Infrequently, the manifestations of HAE type I and type II first occur during pregnancy[1]
  - Plasma C1-INH levels usually drop during pregnancy, even in women without HAE – therefore it can be more challenging to diagnose HAE type I and II during pregnancy
  - Measurement of C1-INH protein/function and C4 should be interpreted with caution
  - Repeat measurements after birth are recommended to confirm the diagnosis of HAE

C1-INH, C1-esterase inhibitor

1. Maurer *et al. Allergy*. 2022. 2. Caballero *et al. International Journal of Women's Heath*. 2014;6:839–848. 3. Caballero *et al. J Allergy Clin Immunol*. 2012;129(2):308–320.
4. González-Quevedo *et al. J Investig Allergol Clin Immunol*. 2016;26(3):161–167.

5. Which products are typically considered safe to treat acute HAE attacks in pregnant patients?

A. Plasma-derived C1-INH
B. Icatibant
C. Ecallantide
D. Solvent detergent-treated plasma
E. Fresh frozen plasma

C1-INH, C1-esterase inhibitor

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C1-INH, C1-esterase inhibitor

Feedback

- Plasma-derived C1-INH (pdC1-INH) concentrate is recommended as first-line on-demand therapy for pregnant or breastfeeding patients with HAE[1,2]
- Pre-procedural prophylaxis in pregnancy is recommended, preferably with C1-INH, for interventions that come with a risk of attacks such as chorionic villus sampling, amniocentesis, and induced surgical abortion[1]
  - Alternatively, C1-INH should be available and administered immediately at the onset of an attack
- The use of icatibant is contraindicated in pregnancy; however, there are isolated case reports with no maternal or fetal adverse effects reported[1, 3–6]
- The use of ecallantide is not recommended in pregnant patients[1,7]
- Solvent detergent-treated plasma may be used when pdC1-INH is not available and fresh frozen plasma when solvent detergent-treated plasma is not available[1]

C1-INH, C1-esterase inhibitor

1. Maurer *et al. Allergy*. 2022. 2. CSL Behring. Berinert 500/1500 Summary of Product Characteristics. 2021. 3. Takeda UK Ltd. Firazyr. Summary of Product Characteristics. 2021. 4. Kaminsky *et al. Allergy Rhinol (Providence)*. 2017;8(3):178–181. 5. Farkas *et al. J Obstet Gynaecol Res*. 2016;42(8):1026–1028. 6. Zanichelli *et al. J Investig Allergol Clin Immunol*. 2015;25(6):447–449. 7. Takeda. Ecallantide. Summary of Product Characteristics. 2014.

6. Which products are recommended for LTP treatment of HAE in pregnancy?

A. Plasma-derived C1-INH

B. Androgens

C. Berotralstat

D. Lanadelumab

C1-INH, C1-esterase inhibitor

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C1-INH, C1-esterase inhibitor

Feedback

- Long-term prophylaxis may become indicated during pregnancy, especially in women experiencing an increase of attack frequency. In these women, C1-INH is considered safe and effective[1,2]
  - Plasma-derived C1-INH concentrate is recommended as first-line therapy (on-demand, STP and LTP) for pregnant or breastfeeding patients with HAE[1–3]
- Androgens are contraindicated in pregnant patients with HAE[4]
  - The most common adverse effect is masculinization of the female fetus[4]
  - Androgens are secreted in breast milk[1,4]
  - Breastfeeding should be discontinued before androgens are introduced postpartum[1,4]
- The use of berotralstat and lanadelumab is not recommended in pregnant patients[5,6]
- Antifibrinolytics have been considered safe during pregnancy and breastfeeding, and may be considered if C1-INH is unavailable for LTP, but efficacy is not proven[7]

C1-INH, C1-esterase inhibitor; LTP, long-term prophylaxis; STP, short-term prophylaxis

1. Maurer *et al. Allergy*. 2022. 2. CSL Behring. Berinert 2000/3000 Summary of Product Characteristics. 2020.
3. CSL Behring. Berinert 500/1500 Summary of Product Characteristics. 2021. 4. Sanofi. Danazol Summary of Product Characteristics. 2019.
5. BioCryst UK Ltd. Orladeoya (berotralstat). Summary of Product Characteristics. 2021.
6. Takeda. Takhzyro (lanadelumab). Summary of Product Characteristics. 2021. 7 Rivopharm UK Ltd. Tranexamic acid. Summary of Product Characteristics. 2018.

Concerns with labor/delivery and breastfeeding

- Sarah explains that she is particularly concerned with regards to labor/delivery and breastfeeding
- She is worried that labor or the trauma of the delivery may trigger an HAE attack
- She also wonders whether it is safe to breastfeed whilst she is receiving her HAE treatment

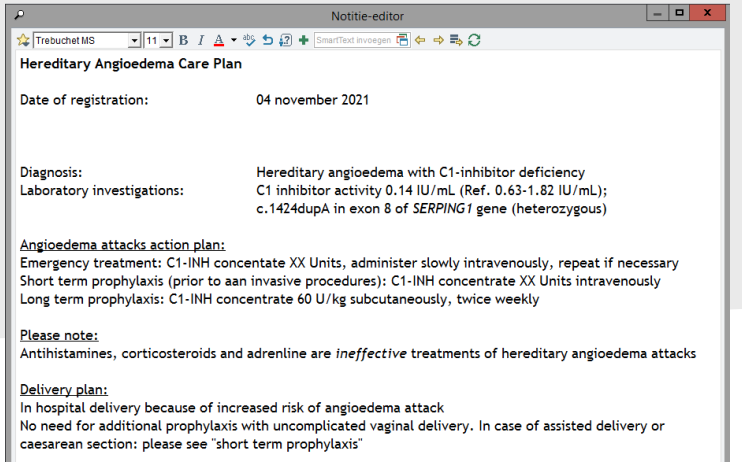
7. What special recommendations should be considered for a care plan regarding labor and delivery?

A. In-hospital delivery

B. No need for pre-procedural prophylaxis if unassisted vaginal delivery

C. Acute treatment must be readily available

D. All of the above



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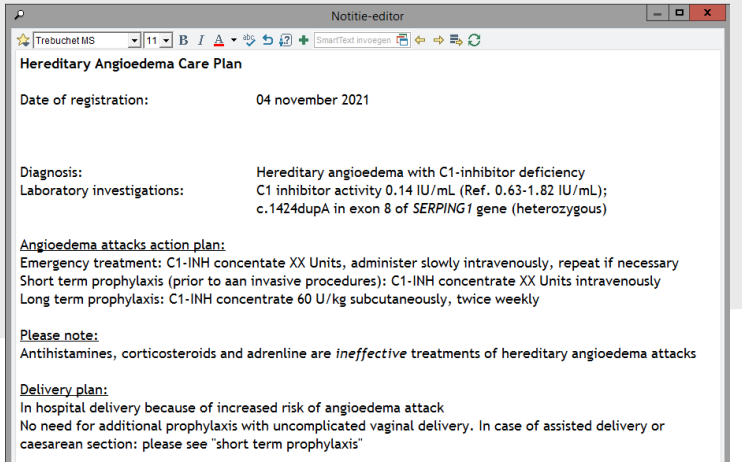
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No need for additional prophylaxis with uncomplicated vaginal delivery. In case of assisted delivery or caesarean section: please see "short term prophylaxis"

Feedback

WAO/EAACI guidelines recommend that:[1]

- Childbirth should be managed in the hospital setting unless robust measures for the prompt and effective treatment of HAE attacks are available
- Pre-procedural prophylaxis before uncomplicated natural delivery is not mandatory, but guidelines recommend that C1-INH concentrate should be available for immediate on-demand use
- Vaginal delivery is preferred because:
  - Surgery or general anesthesia may involve endotracheal intubation, which can trigger laryngeal attacks[1]
  - Attacks during vaginal delivery are rare[2] and will usually occur within the first 48 hours after delivery[1]
  - Published studies have reported that less than 10% of attacks in pregnant women occurred during labor/delivery[3–5]
- Pre-procedural prophylaxis with C1-INH and epidural anesthesia should be used before a cesarean section, and intubation should be avoided if possible. If intubation is planned, pre-procedural prophylaxis is mandatory[1]
- Close follow up is recommended for at least 72 hours postpartum after uncomplicated vaginal delivery[1]

C1-INH, C1-esterase inhibitor; EAACI, European Academy of Allergy and Clinical Immunology; WAO, World Allergy Organization

1. Maurer *et al. Allergy*. 2022. 2. Caballero *et al. Int J Womens Health*. 2014;6:839–848. 3. Grivcheva-Panovska *et al. Mayo Clin Proc Innov Qual Outcomes*. 2020;4(5):595–600. 4. Bouillet *et al. Am J Obstet Gynecol*. 2008;199(5):484. 5. Czaller *et al. Eur J Obstet Gynecol Reprod Biol*. 2010;152(1):44–49.

8. Breastfeeding may be associated with an increased number of maternal attacks in HAE

A. True

B. False

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A. True

B. False

Feedback

- Breastfeeding may be associated with increased attack frequency in the mother[1]
  - Ceasing breastfeeding may alleviate attack frequency; however, breastfeeding is still recommended based on the benefits provided to the baby
- Plasma-derived C1-INH is the recommended therapy for on-demand treatment, STP or LTP when breastfeeding[1–3]
- Androgens and antifibrinolytics are secreted in breast milk[1,4,5]
  - Androgens should not be used when breastfeeding, due to the potential for androgenic effects in the infant[4]; however, tranexamic acid has been found to be safe during breastfeeding

C1-INH, C1-esterase inhibitor; LTP, long-term prophylaxis; STP, short-term prophylaxis

1. Maurer *et al. Allergy*. 2022; 2. CSL Behring. Berinert 500/1500 Summary of Product Characteristics. 2021.
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5. Rivopharm UK Ltd. Tranexamic acid. Summary of Product Characteristics. 2018.

Take-home messages[1]

- Plasma-derived C1-INH is the preferred therapy during pregnancy and lactation for on-demand, STP and LTP
- Several factors can contribute to an increase in HAE attack frequency during IVF and pregnancy (i.e., increased estrogen levels, ovulation and stress)
- In healthy women, C1-INH plasma levels decrease during pregnancy and return to normal after delivery
  - For the purpose of diagnosing HAE type I and II during pregnancy, measurement levels should be interpreted with caution. It is recommended to repeat the measurements after birth to confirm the diagnosis of HAE
- It is recommended to manage childbirth in a hospital setting and vaginal delivery is preferred to minimize the risk of attacks
  - Pre-procedural prophylaxis before uncomplicated natural delivery is not mandatory, but C1-INH concentrate should be available for on-demand treatment
    - Pre-procedural prophylaxis with C1-INH and epidural anesthesia is recommended before a cesarean section, and intubation should be avoided if possible. If intubation is planned, pre-procedural prophylaxis is mandatory
- Breastfeeding may also be associated with an increased number of maternal attacks but is still recommended based on the benefits it provides to the baby
- Personalized treatment and delivery plans are highly recommended

C1-INH, C1-esterase inhibitor; LTP, long-term prophylaxis; STP, short-term prophylaxis

1. Maurer *et al. Allergy*. 2022.