demonstrated what we believe to be previously undocumented findings of a caudally displaced costotransverse and cranially displaced costovertebral joint (the opposite of the classically described findings), which affected therapeutic options.

Osteopathic therapy that mobilizes and pushes the first rib in the caudal direction is a standard therapy [3]. In this patient, however, the rib would need to be "grabbed" and pulled upward, which would likely require general anesthesia for the patient to tolerate and to achieve adequate muscle relaxation. Surgical rib removal could also be considered. The patient declined further treatment.

Pain practitioners should be aware of this possibility in patients with cervicalgia with symptomatology typical of first rib subluxation.

Authors' Contributions

All authors contributed to the conception and authorship of the article. Peter Van de Putte and Peter De Mulder provided Figure 1. Peter De Mulder also contributed to clinical care.

References

1. Kamkar A, Cardi-Laurent C, Whitney SL. Conservative management of superior subluxation of the first rib. J Sport Rehabil 1992;1(4):300–16.
2. Kaczynski J, Dillon M, Hilton J. Superior subluxation of an anterior end of the first rib in a trauma patient. BMJ Case Rep 2012;2012(1):bcr0220125796.
3. Stoddart S, Handy M, Cleland P, et al Traumatic dislocation of the first rib: A case report and review of the literature. Emerg Med Australas 2017;29(6):746–8.

Pain Medicine, 22(8), 2021, 1878–1882
doi: 10.1093/pm/pnaa457
Advance Access Publication Date: 26 March 2021
Resident & Fellow Forum

Obstetric Anesthetic Management for Parturients with Hereditary Angioedema: A Case Report and Suggested Protocol

Kathryn J. Clark , MB, BCh, BAO* Hans P. Sviggum, MD* Adam K. Jacob, MD* Katherine W. Arendt, MD* Gerald W. Volcheck, MD† Linda M. Szymanski, MD, PhD‡ and Emily E. Sharpe, MD*

*Departments of Anesthesiology and Perioperative Medicine; †Medicine, Division of Allergic Diseases, and; ‡Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to: Kathryn J. Clark, MB, BCh, BAO, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First Street SW Rochester, MN 55905, USA. Tel: 507 284 2511; E-mail: clark.kathryn1@mayo.edu.

Abstract

Abstract. Hereditary angioedema (HAE) is a disease manifested by repeated episodes of localized submucosal or subcutaneous edematous episodes, potentially triggered by emotional stress, mechanical trauma, or intake of estrogens. We present our experience managing two parturients with HAE. Multidisciplinary care is essential for planning and executing the specialized care of these patients, and management included extensive planning among obstetric, anesthesiology, and allergy and immunology teams. Pregnancy has been shown to have a variable effect on triggering HAE episodes. First-line treatment includes C1 esterase inhibitor concentrate, which can also be used for prophylaxis in high-risk patients. Neuraxial analgesia is recommended to avoid general anesthesia and was established early in both individuals. Vaginal delivery was well tolerated without need for emergent treatment for angioedema symptoms.

Key words: Angioedema; Pregnancy; Epidural; Anesthesia; C1 Esterase Inhibitor Deficiency; Hereditary Angioedema

Introduction

Hereditary angioedema (HAE) is characterized by recurrent edematous episodes typically affecting the subcutaneous or submucosal tissues, potentially triggered by emotional stress, mechanical trauma, or intake of estrogens. Upper respiratory or laryngeal involvement has the potential to cause fatal upper airway obstruction. Although pregnancy has variable effects on HAE, labor and delivery rarely provoke an edematous episode, despite substantial mechanical trauma. When angioedema

occurs, it typically occurs immediately after or within 48 hours of delivery [1]. We report two patients with HAE experiencing three deliveries and propose an anesthetic management protocol for the peripartum management of patients with HAE.

Case Descriptions

Case One

A 26-year-old G1P0 presented for obstetric anesthesiology consultation with a history of recurrent throat swelling, extremity swelling, and abdominal angioedema starting at 12 years of age. The patient had a history of a tonsillectomy in childhood without issue; however, the tonsillectomy occurred before the onset of her angioedema symptoms. She denied requiring airway instrumentation for prior airway obstruction. The patient reported a strong family history of angioedema in multiple relatives. To her knowledge, female relatives had not experienced peripartum complications.

Throughout her pregnancy, she presented multiple times to the hospital with angioedema. She did not use any maintenance therapy throughout her pregnancy. She was seen in allergy and immunology consultation at 33 weeks' gestation. Laboratory studies confirmed HAE type 1. She was seen in obstetric anesthesiology consultation at 34 weeks' gestation, and her care was discussed in multidisciplinary rounds that included obstetric anesthesiology and maternal fetal medicine. Delivery was recommended if the patient were to experience a flare after 37 weeks' gestation; otherwise, the patient was to be induced at 39 weeks with planned prophylactic administration of human C1 esterase inhibitor (C1-INH) concentrate (1,000 IU intravenously) 1 hour before anticipated delivery, with further dosing (20 IU/kg) for a flare.

The patient was admitted at 39 weeks for a risk-reducing induction. Airway examination at the time of admission revealed Mallampati II with full neck range of motion and mouth opening >3 cm, with no evidence of angioedema. A dural puncture epidural (DPE) was placed, which is used frequently at our institution for the associated benefits of placement reassurance and improved sacral spread [2]. Programmed intermittent bolus with patient-controlled epidural analgesia with 0.1% bupivacaine and 2 μg/mL fentanyl was initiated, which is the standard epidural solution at our institution. The patient progressed through labor uneventfully and ultimately declined prophylactic treatment with C1-INH, for the stated reason of high medication cost. The risks of declining this medication for prophylaxis were discussed, and it was agreed that C1-INH would be given as rescue therapy if needed. She had a spontaneous vaginal delivery, without evidence of angioedema symptoms throughout the intrapartum and postpartum periods.

The patient's second delivery course 13 months later was similar to her first. She required multiple visits to the emergency department throughout her pregnancy for angioedema symptoms. She underwent induction of labor at 39 weeks' gestation. Early neuraxial analgesia was achieved with a DPE. She again declined prophylactic C1-INH and had a spontaneous vaginal delivery without angioedema symptoms peripartum.

Case Two

A 30-year-old G4P1 woman with a history of HAE type III, based on history of recalcitrant recurrent angioedema with response to C1-INH, was seen in consultation at 28 weeks' gestation by obstetric anesthesiology. She was maintained on long-term prophylactic recombinant C1-INH at home two to three times per week. Previous edematous episodes had consisted of hand, feet, abdominal, and tongue swelling. She had never been intubated for angioedema and had undergone procedures requiring anesthesia without complication. During pregnancy, she had increased her prophylaxis regimen to daily infusions of recombinant C1-INH, as per the recommendation of her allergist outside of our institution. She was admitted multiple times throughout her pregnancy with concerns for preterm labor. She did not report any angioedema episodes from the onset of pregnancy. Laboratory studies obtained at 34 weeks' gestation demonstrated normal values of C1-INH antigen and function.

The patient was induced at 34 weeks and 4 days' gestation for intrauterine growth restriction and gestational hypertension. Airway examination at the time of admission revealed Mallampati I with full neck range of motion and mouth opening >3 cm, with no noted angioedema. She continued her home dose of recombinant C1-INH throughout the peripartum period, with plans to give 20 IU/kg of plasma-derived C1-INH for an acute flare-up. A DPE was placed, and programmed intermittent bolus with patient-controlled epidural analgesia with 0.1% bupivacaine and 2 μg/mL fentanyl was initiated. She had a spontaneous vaginal delivery. There was no evidence of angioedema symptoms throughout the intrapartum and postpartum periods, and therefore she did not receive additional C1-INH peripartum.

Discussion

This case report describes three deliveries involving patients with HAE type I and type III. HAE is classically caused by a quantitative (type I) or functional (type II) deficiency in C1 esterase inhibitor (C1-INH), although a distinct subtype (HAE type III) was described in 2000 (Table 1) [1, 3, 4]. Clinically, this subtype is indistinguishable from others; however, it is often referred to as estrogen-dependent HAE or HAE with normal C1 activity [3]. The C1-inhibitor protein is a serine protease inhibitor involved in controlling vascular permeability and the activation of the complement, coagulation, contact, and fibrinolytic systems. Lack of C1-INH results in an

Table 1.. Features of HAE

	HAE I	HAE II	HAE III
Main feature	Quantitative deficiency	Functional deficiency	Normal-functioning C1-INH
C1-INH level	Low	Normal/high	Normal
C1-INH function	Low	Low	Normal
Influence of gender	Women = men	Women = men	Women > men
Incidence among HAE	80–85%	15–20%	Extremely rare

Table 2.. Medical management of HAE

Medication	Mechanism of Action	Indication	Use in Pregnancy	Dose	Route of Administration	Relative Cost
Human plasma–derived C1-INH concentrate	C1-INH replacement	Acute flare-up, STP, LTP	First-line in pregnancy	Acute flare-up: 20 IU/kg; STP: 1,000 IU; LTP: 40–60 U/kg twice weekly	IVSC available for LTP	High
Recombinant C1-INH	C1-INH replacement	Acute flare-up	Category B pregnancy	50 IU/kg[†]	IV	High
Icatibant*	Bradykinin B2 receptor antagonist	Acute flare-up	Not studied/approved in pregnancy	30 mg every 6 h, maximum 3 doses in 24 h	SC	High
Ecallantide*	Kallikrein inhibitor	Acute flare-up	Not studied/approved in pregnancy	30 mg, can repeat once within 24 h	SC	High
Tranexamic acid	Inhibition of fibrinolysis	LTP	Category B pregnancy; alternative if C1-INH not available	2–5 g/day	Oral, IV	Low
Fresh frozen plasma	C1-INH replacement	Acute flare-up, STP	Alternative if C1-INH not available	2 units	IV	Moderate

IV=intravenous; SC=subcutaneous.
*Limited data available on use in pregnant patients.
[†]Maximum of 4,200 units.

excessive production of the vasoactive peptide, bradykinin, which is the main mediator responsible for increased vascular permeability and angioedema. The combined prevalence of HAE I and II is estimated to be around 1:50,000, with HAE III thought to be much less prevalent, though its true prevalence is unknown [4].

Many triggering factors have been demonstrated to precipitate edematous episodes in patients with HAE, and pregnancy has been shown to have a variable effect on HAE-C1-INH edematous attacks [1]. However, an increase in episodes during pregnancy has been demonstrated and is thought to be secondary to pregnancy-related hormonal changes [5]. In one of the largest studies of pregnancy and HAE, angioedema episodes tended to occur more frequently in pregnancy but did not appear to increase in severity [6]. There is an association between onset of symptoms early in life and more frequent and more severe attacks during pregnancy [1, 7].

Edematous HAE episodes can be treated with plasma-derived C1-INH (FDA Pregnancy Category C, according to the former classification system), recombinant C1-INH, icatibant acetate, or ecallantide (Table 2) [1, 8, 9]. Of note, there are limited data on the use of recombinant C1-INH (FDA Pregnancy Category B) and icatibant acetate (FDA Pregnancy Category C) in pregnancy, and no data are available on the use of ecallantide (FDA Pregnancy Category C) during pregnancy. Administration of 1,000 IU of C1-INH concentrate should be considered 1 hour before expected delivery. Additional C1-INH should be administered at a dose of 20 IU/kg if the patient develops acute angioedema. In cases in which the first-line plasma-derived C1-INH concentrate is not available, the treating physician must judge whether the benefits outweigh the possible risks of the alternative therapies.

Patients with HAE can also be treated with short-term prophylaxis (STP) and long-term prophylaxis (LTP). STP is used before surgery, procedures, or anesthetic techniques that may impact the upper aerodigestive tract. For example, administration of plasma-derived C1-INH has been recommended if forceps- or vacuum-assisted delivery or cesarean delivery is performed. Fresh frozen plasma can be

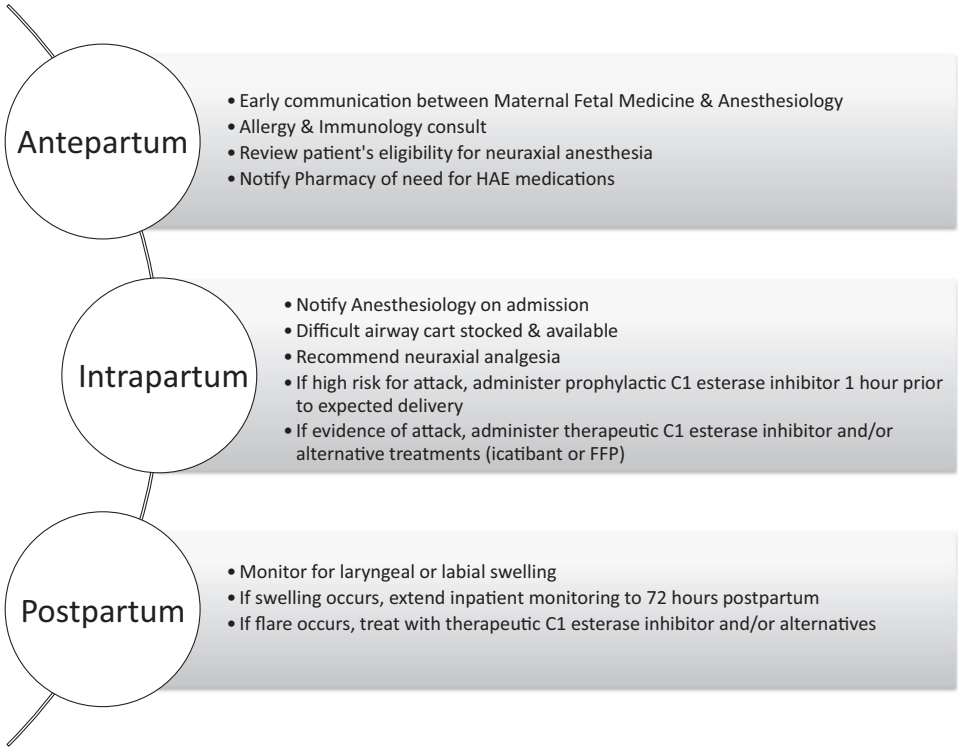

Figure 1. Anesthetic management of pregnant women with HAE. FFP=fresh frozen plasma.

used for STP if inhibitor concentrate is not available [1]. LTP is used to manage angioedema in patients whose symptoms are poorly controlled despite appropriate on-demand therapy. C1-INH is the first-line treatment for LTP. Tranexamic acid has been used previously for LTP when C1-INH has been unavailable, but a consensus has not been reached on the overall efficacy of tranexamic acid or its use in pregnancy. Lanadelumab and attenuated androgens are alternative medications that have been used in LTP and STP, but lanadelumab has not been studied in pregnancy, and attenuated androgens are contraindicated in pregnancy [4]. Unfortunately, treatment for HAE can be costly, and the patient from Case One ultimately declined prophylactic treatment for this reason.

Although neither of our patients experienced an intrapartum flare-up of HAE, it is important for the obstetric anesthesiologist to be prepared to treat an acute flare-up. We propose an obstetric anesthetic management protocol for patients with HAE (Figure 1) consistent with previously published obstetric practice and HAE guidelines [1, 4, 10]. Parturients with HAE should deliver in hospitals with a multidisciplinary team including obstetric anesthesiology, maternal fetal medicine, and allergy and immunology [1, 10]. Planning for these patients should include notification of pharmacy of the need for HAE medications before admission. Although routine prophylaxis before uncomplicated vaginal deliveries is not recommended, plasma-derived C1-INH should be immediately available in the labor and delivery unit for an angioedema flare-up, intubation, or emergent cesarean or procedural delivery [1, 10]. Patients with HAE should be reviewed for eligibility for neuraxial anesthesia in the antepartum period, and anesthesia should be notified on the patient's admission to the labor and delivery ward. Of note, vaginal delivery is preferred, with cesarean delivery reserved for obstetric indications only [1, 10]. An epidural is recommended to provide labor analgesia and avoid conversion to general anesthesia if cesarean delivery is necessary. In our institution we frequently use both the DPE and combined spinal-epidural techniques because of evidence of improved sacral spread and reduced unilateral analgesia [2]. If a parturient develops airway edema during labor, maternal hypoxia could lead to fetal compromise and necessitate an emergent cesarean delivery. Airway instrumentation should be avoided, as mucosal trauma may initiate angioedema, and difficult airway equipment should be readily available if airway edema occurs. At baseline, pregnant women are at increased risk of difficult intubation, and the presence of impending or present airway obstruction could further complicate airway management. If intubation fails, emergency tracheostomy or cricothyroidotomy may be required.

Patients with HAE who required therapeutic treatment and those who demonstrate marked perineal swelling after vaginal delivery should be considered high risk, and close monitoring, including examination for evidence of angioedema for 72 hours, is recommended [1, 10]. Before hospital discharge, patients should be informed of their increased risk of postpartum swelling, and a treatment plan should be discussed.

In conclusion, multidisciplinary care and close communication between obstetric, anesthesiology, allergy and immunology, and pharmacy teams are essential for planning and executing the specialized care of patients with HAE. Plasma-derived C1-INH concentrate is the best therapy for on-demand treatment, STP, and LTP in pregnancy. Neuraxial analgesia is recommended to avoid general anesthesia in case of emergent cesarean delivery. Patients with significant perineal edema or an acute flare-up during delivery should be observed for at least 72 hours postpartum.

Board-Style Questions

1. Which of the following medications is considered first-line treatment in a parturient with a history of HAE who presents in active labor and is at high risk for an angioedema flare-up?

A. Tranexamic acid
B. C1 esterase inhibitor
C. Fresh frozen plasma
D. Icatibant
E. Diphenhydramine

Answer: B. C1 esterase inhibitor.

For a parturient at high risk of angioedema flare-up, administration of 1,000 IU of C1-INH concentrate should be considered 1 hour before expected delivery [1, 3, 9]. Alternative medications such as icatibant [7, 8] (Answer D) or fresh frozen plasma [1] (Answer C) should also be available as second-line therapy. Tranexamic acid (Answer A) is not recommended as on-demand treatment or STP in these patients, and a consensus has not been reached on its overall efficacy or use in pregnancy [1, 3, 9]. Although antihistamines, such as diphenhydramine (Answer E), corticosteroids, and epinephrine treat histamine-related angioedema, they are not supported by the evidence for treatment of HAE attacks [3].

2. In a parturient with HAE, which of the following statements is most accurate?

A. Caesarean delivery is automatically indicated in these patients.
B. General anesthesia is the safest anesthetic plan for these patients.
C. Icatibant is the first-line treatment for those who present with an angioedema flare-up.
D. An epidural is recommended to provide labor analgesia.
E. Pregnancy has no effect on HAE attacks.

Answer: D. An epidural is recommended to provide labor analgesia.

An epidural is recommended to provide labor analgesia and avoid conversion to general anesthesia if cesarean delivery is necessary [1]. General anesthesia (Answer B) with instrumentation should be avoided, as mucosal trauma may initiate angioedema [9]. Vaginal delivery is preferred, with cesarean delivery (Answer A) reserved for obstetric indications only. C1 esterase inhibitor, not icatibant (Answer C), is the first-line treatment for those who present with an angioedema flare-up or those at high risk of flare-up before delivery or procedure [1,3,9]. Pregnancy has a variable effect on HAE-C1-INH edematous attacks [1], although an increase in attack rate during pregnancy has been demonstrated, which is thought to be secondary to pregnancy-related hormonal changes [4].

References

1. Caballero T, Farkas H, Bouillet L, et al 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 2012;129(2):308–20.
2. Chau A, Bibbo C, Huang CC, et al Dural puncture epidural technique improves labor analgesia quality with fewer side effects compared with epidural and combined spinal epidural techniques: A randomized clinical trial. Anesth Analg 2017;124(2):560–9.
3. Miranda AR, Fusel de Ue AP, Sabbag DV, et al Hereditary angioedema type III (estrogen-dependent) report of three cases and literature review. An Bras Dermatol 2013;88(4):578–84.
4. Betschel S, Badiou J, Binkley K, et al The International/Canadian hereditary angioedema guideline. Allergy Asthma Clin Immunol 2019;15(1):72.
5. Martinez-Saguer I, Rusicke E, Aygoren-Pursun E, et al Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. Am J Obstet Gynecol 2010;203(2):131.e1–7.
6. Gonzalez-Quevedo T, Larco JI, Marcos C, et al Management of pregnancy and delivery in patients with hereditary angioedema due to C1 inhibitor deficiency. J Investig Allergol Clin Immunol 2016;26(3):161–7.
7. Czaller I, Visy B, Csuka D, et al 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 2010;152(1):44–9.
8. Hakl R, Kuklinek P, Krcmova I, et al Treatment of hereditary angioedema attacks with icatibant and recombinant C1 inhibitor during pregnancy. J Clin Immunol 2018;38(7):810–5.
9. Kaminsky LW, Kelbel T, Ansary F, Craig T. Multiple doses of icatibant used during pregnancy. Allergy Rhinol (Providence) 2017;8(3):178–81.
10. Maurer M, Magerl M, Ansotegui I, et al The international WAO/EAACI guideline for the management of hereditary angioedema: The 2017 revision and update. Allergy 2018;73(8):1575–96.