

Use of pdC1-INH concentrate for long-term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH



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Clinical Implications

- Therapeutic options for hereditary angioedema with normal C1 inhibitor (C1-INH) are scarce. Plasma-derived C1-INH may be effective and safe for long-term prophylaxis in hereditary angioedema with normal C1-INH during pregnancy.

TO THE EDITOR:

Hereditary angioedema (HAE) is characterized by recurrent angioedema attacks with involvement of multiple organs, which are induced by genetic mutations that result in increased bradykinin concentration in the tissues. HAE is a neglected disease presenting high morbidity and mortality, especially if not adequately treated. Patients live with the risk of having laryngeal angioedema that can lead to death by asphyxiation. Furthermore, abdominal attacks are very disabling and patients often inadvertently undergo exploratory laparotomies.¹⁻³

C1 inhibitor (C1-INH) deficiency was the first biochemical change associated with HAE. C1-INH is a serine protease inhibitor from the SERPIN superfamily that participates in regulating the complement, contact, coagulation, and fibrinolysis systems. Patients with HAE with C1-INH deficiency (C1-INH HAE) have low levels of C1-INH or a dysfunctional protein resulting in overactivation of the contact system (kallikrein-kinin system) and increased bradykinin production.¹⁻³ In 2000, Bork et al⁴ identified a new subset of patients with HAE with normal C1-INH concentration and function (HAE with normal C1-INH, previously designated as HAE Type-III). A portion of these patients, which is around 50% in Brazil, presents mutations of the gene coding for coagulation factor XII (FXII). Studies showed that mutation in FXII may lead to gain-of-function changes or render it abnormally sensitive to plasmin cleavage, causing excessive bradykinin production. Interestingly, there is evidence that lysine analogs, including tranexamic acid and epsilon aminocaproic acid, may attenuate FXII mutants abnormally sensitive to plasmin, supporting their use in these patients.^{1,5,6} Recently, a novel type of HAE with normal C1-INH was described in patients belonging to 4 families who had a missense mutation in the plasminogen gene.^{1,6}

Patients with HAE, especially those with normal C1-INH, show worsening symptoms in hyperestrogenic conditions such as that which occurs during pregnancy or exogenous estrogen intake, like contraception or hormone replacement therapy. The

mechanisms underlying this deterioration are only partially understood. The promoter region of the FXII gene contains an estrogen-responsive element, and increases in FXII mRNA transcription in response to estrogen have been demonstrated in previous studies. It is likely that estrogen also contributes to the regulation of B2 bradykinin receptor expression, modulates the kallikrein-kinin cascade, and lowers C1-INH levels. IL-1, TNF- α , and estrogen stimulate the release of Hsp90 and may activate the prekallikrein-high-molecular-weight kininogen (HK) complex to generate kallikrein and bradykinin.^{5,6}

Symptoms tend to worsen during pregnancy, especially in the first trimester, when women receiving long-term prophylaxis discontinue their treatments, and blood estrogen levels are higher.^{1,5,6} Therapy for HAE with or without C1-INH deficiency is limited during pregnancy, delivery, and postpartum. Plasma-derived C1-INH (pdC1-INH) concentrate is the only drug recommended during these periods, according to all published data.^{1-3,7}

The objective of long-term HAE prophylaxis is to reduce the frequency and severity of attacks, improving patients' quality of life. Worldwide, 3 treatment modalities for long-term prophylaxis have been used: attenuated androgens, antifibrinolytic agents, and pdC1-INH.¹⁻³ We reviewed the small case series reported in the literature assessing the use of pdC1-INH for long-term prophylaxis of C1-INH HAE during pregnancy. The combined data suggest that this therapy is effective and safe.⁷⁻⁹ Attenuated androgen use is not recommended during pregnancy, because these drugs cross the placental barrier and may result in virilization of the fetus, leading to female pseudohermaphroditism. Tranexamic acid also crosses the placental barrier and may have side effects that affect the fetus, although the risk is lower and such effects are less severe than those of attenuated androgens. Therefore, tranexamic acid can be used during pregnancy when pdC1-INH concentrate is not available, but with caution due to its prothrombotic effects, especially in patients with a personal and/or family history of thromboembolism.^{1,7-9}

HAE with normal C1-INH concentration and function has a later onset, longer disease-free intervals, more frequent facial and tongue swelling, and less frequent attack of abdominal pain. Most patients affected are women, particularly pregnant women or those exposed to exogenous estrogen.^{5,6} The β 2 bradykinin receptor antagonist icatibant has been prescribed to treat acute attacks and pdC1-INH has been used off-label to treat acute attacks and in short-term prophylaxis, even knowing that these patients have normal functional and quantitative C1-INH levels. Observational studies have shown the efficacy of these treatments.^{6,9,10}

The experience with long-term prophylaxis in HAE with normal C1-INH is restricted to case reports only. There is some evidence suggesting that tranexamic acid reduces the frequency and severity of attacks and may be considered a suitable treatment option; furthermore, patients with HAE with normal C1-INH may respond better to antifibrinolytic agents than patients with C1-INH HAE. Progestins have also been recommended as a treatment for HAE with normal C1-INH, and studies have shown their effectiveness.^{5,6,9,10} Because these

TABLE I. Efficacy and safety of long-term prophylaxis in hereditary angioedema with normal C1-INH in pregnancy

Patient no.	No. of attacks before pregnancy	No. of attacks during pregnancy		No. of attacks after pregnancy	Pregnancy outcome	Route of birth	Dose of pdC1INH during long-term prophylaxis/gestational age at initiation
		Before pdC1INH	During pdC1INH				
1	Once a year	Once a week	Once a month	None	No attacks/healthy baby	Vaginal	1,000 IU once a week/20 wk
2	Twice a year	Once a week	None	None	No attacks/healthy baby	Cesarean	1,000 IU twice a week/32 wk
3	Once a year	Twice a week	None	One postpartum	No attacks/healthy baby	Cesarean	1,000 IU twice a week/27 wk

patients do not have deficiency of C1-INH, attenuated androgens and pdC1-INH replacement have not been indicated for them. As far as we know, there is no case reported in the literature of long-term prophylaxis with pdC1-INH properly done during pregnancy in HAE with normal C1-INH. Only an intention of long-term prophylaxis was reported in a pregnant woman, who received 3 doses of 500 U of pdC1-INH, twice monthly. The treatment was ineffective.¹⁰

The study hypothesis is that an extra therapeutic dose of C1-INH leading to a supraphysiological serum concentration of this protein could increase the inhibition of bradykinin production, which is increased in patients with HAE with normal C1-INH. We performed a prospective open trial to assess the efficacy and safety of pdC1-INH for long-term prophylaxis of HAE with normal C1-INH in pregnancy.

Three pregnant women with HAE with normal C1-INH and frequent attacks were included in the study. The study protocol was approved by the institutional review board at *Hospital das Clínicas* of University of São Paulo Medical School (CAPPesq) and all patients provided written informed consent.

As expected, the 3 patients had worsening of HAE during pregnancy and they were having frequent attacks (Table I). The first patient had recurrent angioedema once a year since she was 15 years old. Most attacks affected the extremities and lasted 5 days, but she also reported 2 oropharyngeal attacks with hospitalization in the intensive care unit. The diagnosis of HAE with normal C1-INH was made when she was 28 years old and she had never received specific treatment for the disease. The patient had normal C4 and normal functional and quantitative C1-INH levels, positive family history for HAE, and the c.983C>A FXII mutation (p.Thr328Lys). Three months after the diagnosis, our patient became pregnant. The disease got worse during pregnancy, with 1 attack per week since the first trimester. At 20 weeks of pregnancy, long-term prophylaxis was started with pdC1-INH (1,000 IU once a week, which was the dose available in our service at that time), and her HAE was controlled. She still had attacks affecting her extremities, but they were milder, less frequent (once a month), and lasted less than 24 hours. The patient also had 2 oropharyngeal attacks, which were controlled in less than 24 hours, that required hospitalization in the infirmary. Short-term prophylaxis before delivery was not prescribed and our patient did not have an HAE attack during childbirth, giving birth to a healthy baby through vaginal delivery.

The second patient had recurrent angioedema in extremities and face, twice a year, since she was 17 years old. She reported 1 hospitalization in the intensive care unit. Like the first patient, she had normal C4 and normal functional and quantitative C1-INH levels, positive family history for HAE, and the c.983C>A FXII mutation (p.Thr328Lys). The diagnosis of

HAE with normal C1-INH was made when she was 30 years old and then, she started to take progestins with disease control, without attacks until her pregnancy. Our patient got pregnant and HAE attacks started again, but, now, with an increased rate of 1 attack per week. At 32 weeks of pregnancy, HAE long-term prophylaxis with pdC1-INH (1,000 IU twice a week) was introduced and HAE was controlled. Since then, she had no more attacks and gave birth to a healthy baby through cesarean section, without using short-term prophylaxis. She remained asymptomatic after pregnancy and did not need any more medication.

The third patient had recurrent angioedema in extremities and abdomen once a year. She was diagnosed with HAE with normal C1-INH at age 27 years, when she started to take oral contraceptives. She had normal C4 and normal functional and quantitative C1-INH levels and positive family history for HAE (her mother also had angioedema attacks during pregnancy). Although no FXII mutation was detected in the genetic analysis, the diagnosis of HAE with normal C1-INH was arrived at on the basis of typical personal and family history associated with normal C1-INH dosages. During pregnancy, abdominal angioedema attacks increased to twice a week, and long-term prophylaxis with pdC1-INH (1,000 IU twice a week) was started at 27 weeks of pregnancy. Since then, the patient had no more attacks during her pregnancy, giving birth to a healthy baby through cesarean section. Because our patient was on long-term prophylaxis, we did not prescribe short-term prophylaxis and she had no attacks during the delivery. However, our patient presented an abdominal attack 2 days later, which was successfully treated with pdC1-INH. Now, she is asymptomatic without treatment.

We observed that after long-term prophylaxis with pdC1-INH, there was a remarkable improvement in disease in all patients, who had no adverse reactions, no peripartum HAE severe attacks, and who gave birth to healthy babies through vaginal or cesarean deliveries (Table I). The unique outcome to verify the efficacy and safety of long-term prophylaxis for HAE is clinical assessment because there is no biomarker to predict HAE attacks. Two of our 3 patients became asymptomatic after they started prophylaxis, and the remaining 1, who received a lower dose of pdC1-INH because of convenience, had an important clinical improvement. We decided to administer pdC1-INH to our patients at least once a week, but trying to deliver the drug twice a week. The rationale for this was based on the long-term prophylaxis for HAE with C1-INH deficiency, although patients with HAE with normal C1-INH have normal protein levels and function. The idea was to give a therapeutic dose to the patients to inhibit the kallikrein-kinin system. The number of patients included in our study is too small to compare the regimen of 1,000 IU twice a week versus 1,000 IU once a week. Some studies have shown a transient deficiency of C1-INH function in

patients with HAE with normal C1-INH during pregnancy and acute attacks.^{9,10} However, providing more C1-INH to a patient with normal levels of functional C1-INH should be done with caution, because the protein is important in complement, fibrinolytic, clotting, and kinin pathways.

After the original description of HAE with normal C1-INH, the knowledge about this HAE subtype has increased and now 2 genetic defects have been identified, mutations in factor XII and plasminogen.^{5,6} However, therapeutic options for HAE with normal C1-INH are scarce and studies investigating improved management should be initiated.

Four variables should be assessed when considering long-term prophylaxis for HAE: frequency, severity, and impact of HAE attacks on patient's quality of life, as well as the availability of proper medications to treat HAE attacks, which may occur even in patients under long-term prophylaxis.¹ The development of new drugs to treat HAE attacks was a major progress. Probably, the next breakthrough development will be new drugs for HAE long-term-prophylaxis. Other products are being investigated for long-term prophylaxis, including pdC1-INH for subcutaneous use, an oral kallikrein inhibitor, and a subcutaneous mAb that inhibits plasma kallikrein.¹

As far as we know this is the first study regarding the use of pdC1-INH for long-term prophylaxis of HAE with normal C1-INH in pregnancy. Although further studies are needed to confirm our findings, the present study suggests that this therapy is efficient and safe. pdC1-INH may be the first choice for long-term therapy of pregnant women with HAE with normal C1-INH who have been presenting with frequent attacks.

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