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Letter to the Editor

Successful long-term prophylaxis with human plasma-derived C1 inhibitor in planning and carrying out pregnancy

Dear Editor,

Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disorder characterized by recurrent attacks of edema in different locations, which may be peripheral or affect internal tissues, as the gastrointestinal tract causing abdominal pain or the upper airways, producing life-threatening asphyxia.¹ The physiopathology of the disease involves several vasoactive peptides, such as bradykinin, which increase endothelial permeability and vascular leakage. The C1 inhibitor (C1-INH) quantitative or qualitative deficiency is the characteristic biomarker of the disease.

The clinical manifestations reduce the physical and social functioning with a significant impact in the quality of life of patients.² Frequent attack triggers are stress, trauma and infections. Direct and indirect costs of the disease have been estimated on 42 000 US\$ a year per patient, but when attack severity and frequency are considered, costs rise up to 92 000 US\$.³

Therapy is addressed by treating or preventing acute attacks and the regimen should always be individualized. Blocking bradykinin receptor agents, kallikrein synthesis inhibitors and C1-INH are used as treatment for acute attacks. Human plasma-derived C1-INH (pdC1-INH) is used as treatment for acute attacks and can also be prophylactically administered either before surgery and invasive procedures or continuously for long-term prophylaxis, when symptoms are frequent and/or severe.¹ Treatment with attenuated androgens for long term prophylaxis has declined lately as their prolonged use have been related to various side effects.^{4,5}

During pregnancy, C1-INH-HAE can worsen due to the increased estrogen levels, although most series describe an unpredictable course.⁶ Even in the same woman, different pregnancies show differences in frequency and severity of angioedema (AE) attacks.⁷

Treatment options during pregnancy are limited. The administration of pdC1-INH has been proven safe and effective in acute attacks, but also as short and long-term prophylaxis.⁸ Fresh frozen plasma can be an alternative for acute attacks, it is cost-effective and safe, as viral transmission is minimal due to effective screening of blood products. However, its content of complement factors has the potential to worsen HAE symptoms. Antifibrinolytic agents such as tranexamic and epsilon aminocaproic acids can be used as prophylaxis; however, potential risks and benefits must be considered, and there are few data on their use during pregnancy. Attenuated androgens such as danazol, are contraindicated during pregnancy, in fact they should be withdrawn at least one month

prior to pregnancy (category X). There is no data about the use during pregnancy of the more recent treatments for C1-INH-HAE such as icatibant acetate, ecallantide or recombinant human C1-INH.⁸

A 34 year-old woman with type I C1-INH-HAE was referred in March 2013 to get support to plan and carry out a second pregnancy. From diagnosis, in 2003, she was treated prophylactically with danazol 200 mg/day, presenting periods of amenorrhea as a side effect of the therapy. In December 2010, she discontinued danazol in order to plan her first pregnancy, which occurred in July 2011 (Table 1). From the first weeks after discontinuing danazol, AE attacks increased in frequency and severity, being almost continuous, requiring repeated on-demand administrations of pdC1-INH (Berinert®, 500–1000 IU). The uncountable attacks, forced her to a prolonged absenteeism from her work. Delivery occurred through the vaginal route without complications, under short-term prophylaxis with Berinert® (1000 IU). She returned to long-term prophylaxis with danazol immediately after delivery however, HAE attacks increased due to psychological stress and common respiratory and urinary infections, presenting frequent combined peripheral (Fig. 1) and abdominal attacks about twice a month and 2 laryngeal attacks, in June and December 2012, both treated with intravenous pdC1-INH.

Blood tests showed low levels of C4 (11 mg/dL) and C1-INH (9 mg/dL) with a functional C1-INH <10%. Blood cell counts, liver function tests and cholesterol were within normal range. Long-term prophylaxis with plasma-derived nanofiltered C1-esterase inhibitor (pdnfc1-INH), Cinryze®, was started in May 2013 and the patient was trained on intravenous self-administration of 1000 IU twice a week. Shortly after initiation of therapy, she referred and important clinical improvement, being practically free of symptoms and danazol was promptly discontinued (Table 1).

The second pregnancy occurred in July 2014. She continued self-administered long-term prophylaxis with pdnfc1-INH with few mild peripheral attacks and a better performance at work. Delivery occurred through vaginal route without complications under prophylaxis with an extra dose of pdnfc1-INH (1000 IU) administered when the labor process started, immediately after arrival into the hospital. She chose not to breastfeed and continued on self-administration of 1000 IU every 4 days of pdnfc1-INH until now, with adequate control of the disease. Peripheral and abdominal attacks recurred 1–2 weeks after any attempt to reduce the dose or frequency of the prophylaxis.

We present the case of a woman with difficulties in getting pregnant due to the side effects of long-term prophylaxis with attenuated androgens for C1-INH-HAE. After starting long-term

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Table 1
Clinical course including pregnancy events, long-term prophylaxis, and therapy for acute attacks.

Time period	Pregnancy events	Long term prophylaxis	Acute attacks frequency	Acute attacks therapy	C4, C1-INH (mg/dl) C1-INH-ACTIVITY (%)
2003–2010	None	Danazol 200 mg/day	<1 attack/month (mild, peripheral and abdominal)	Beriner [®] IV (500 IU) (unfrequently)	C4: 1.9 C1-INH: 11.9 (August 2009)
August 2010 July 2011	Trying to become pregnant	No prophylaxis	>1 attack/week (moderate, peripheral and abdominal)	Beriner [®] IV (500–1000 IU) (abdominal and troublesome attacks)	C4: 2.46 C1-INH: 4.65 (August 2010)
July 2011–March 2012	1st pregnancy	No prophylaxis	≥2 attacks/week (moderate, peripheral and abdominal) *8 months sick leave during pregnancy due to HAE attacks	Beriner [®] IV (500–1000 IU) (abdominal and troublesome attacks)	
March 2012–March 2013	None	Danazol 200 mg/day	2 attacks/month (moderate, peripheral and abdominal; 2 laryngeal attacks)	Beriner [®] IV (1000 IU) (laryngeal and troublesome abdominal attacks)	C4: 11 C1-INH: 9 C1-INH ACTIV: <10 (February 2013)
April 2013 July 2014	Trying to become pregnant	Cinryze [®] 1000 IU twice a week self-administered. Danazol discontinued (July 2013)	<1 attack/month (mild, peripheral and few abdominal)	Treated in few cases by anticipating the following dose of Cinryze [®]	C1-INH: 9 C1-INH ACTIV: 14 (June 2013)
July 2014 April 2015	2nd pregnancy	Cinryze [®] 1000 IU twice a week self-administered.	<1 attack/month (mild, peripheral) *No sick leave during pregnancy	Treated in few cases by anticipating the following dose of Cinryze [®]	
April 2015 March 2017	none	Cinryze [®] 1000 IU/4–5 days self-administered.	<1 attack/month (mild, peripheral and few abdominal)	Treated, when troublesome, by anticipating the following dose of Cinryze [®]	C4: 12 C1-INH: 11 C1-INH ACTIV: 13 (March 2017)

**Fig. 1.** Peripheral angioedema attack during hospitalization for abdominal attack.

prophylaxis with 1000 IU pdnfc1-INH twice a week she could achieve and carry out a successful pregnancy.

C1-INH-HAE itself has not been related to fertility difficulties. However, attenuated androgens, can induce amenorrhea and menstrual irregularities that may hinder conception planning,⁹ as in the case of our patient.

Although no controlled studies have been conducted during pregnancy, there are several case reports about the use of C1-INH as acute treatment, short-term prophylaxis, and long-term prophylaxis during pregnancy.⁸ C1-INH was found to be the safest option for prophylactic and acute treatment as and on demand treatment in pregnant patients with C1-INH-HAE in a retrospective analysis with a total of 16 subjects.¹⁰ A recent report also recommends its use for long-term prophylaxis in severe cases as first line option.⁷

In the reported case, self-administration continued throughout pregnancy without complications.

As reported, patients with C1-INH-HAE have lower scores, both for physical and mental functioning, which directly affects work productivity.² In this case, during the first pregnancy the prolonged sick leave increased the indirect costs of the disease.

Long-term prophylaxis with pdnfc1-INH seems to be a good alternative to accomplish and carry out pregnancy in women with C1-INH-HAE at a reproductive age.

Conflict of interest

The authors have no conflict of interest to declare.

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