Management of pregnancy in hereditary angioedema

Postępowanie w ciąży u chorej z wrodzonym obrzękiem naczynioruchowym

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Summary

Hereditary angioedema due to C1-inhibitor deficiency (HAE) is a rare disease. HAE course can be more severe in female patients due to the activation of contact system by endogen oestrogens. Pregnancy can therefore worsen the disease course in some cases and the HAE management during pregnancy is often a challenge because of the limitation in treatment options. Plasma derived C1 inhibitor concentrate is the election drug for the treatment of acute attacks, short term prophylaxis and long term prophylaxis. In this review we will update the potential variations in HAE clinical course and the indications of the currently available treatments during pregnancy, delivery and breast-feeding.

Keywords: *Hereditary angioedema, pregnancy, delivery, breast-feeding, C1-inhibitor, treatment*

Streszczenie

Wrodzony obrzęk naczynioruchowy z niedoboru C1-inhibitora (HAE) jest chorobą rzadką. U kobiet przebieg HAE może być cięższy z powodu aktywacji przez endogenne estrogeny szlaku zależnego od czynnika kontaktu. Dlatego w części przypadków ciąża może pogarszać przebieg schorzenia, a kontrola objawów HAE podczas ciąży jest często trudna z powodu ograniczeń w możliwych opcjach terapeutycznych. Koncentrat osoczopochodnego C1-inhibitora jest lekiem z wyboru w ostrych napadach oraz profilaktyce krótko- i długoterminowej. W niniejszej pracy dokonano przeglądu aktualnej wiedzy o możliwych zmiennościach w przebiegu klinicznym i wskazaniach obecnie dostępnych w HAE leków w okresie ciąży, porodu i karmienia piersią.

Słowa kluczowe: *wrodzony obrzęk naczynioruchowy, ciąża, poród, karmienie piersią, C1-inhibitor, leczenie*

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Hereditary angioedema due to C1 inhibitor deficiency (HAE) is a rare disease characterized by recurrent and localized acute angioedema (AE) attacks and an estimated prevalence around 1/50,000 inhabitants [1]. C1-inhibitor (C1-INH) deficiency results in an activation of the contact system (formed by plasma coagulation factor XII, plasma prekallikrein and plasma high molecular weight kininogen) and the release of bradykinin (BK), a potent vasodilator [2, 3]. BK binds bradykinin B2 receptors (BKB2R) and produces enhanced vascular permeability, liquid extravasation and swelling [2, 3]. AE attacks are mainly peripheral (extremities, face) and abdominal, but can also be located in upper airways and genitalia [2]. The management of female patients with HAE during pregnancy, labour, delivery and breast-feeding is a challenge due to the possible worsening of the disease during pregnancy and the limitation in the use of specific treatments during these periods, which led to the publication of a consensus document in 2012 [4]. In this manuscript we will update management of HAE during these specific periods.

Role of oestrogens in HAE

Oestrogens, the female sex hormones, can worsen the course of HAE. Thus, female patients with C1-INH-HAE have more frequent AE attacks than male patients and these AE attacks are usually more severe and require more frequently hospitalization than in men [5-7]. HAE course is influenced by the physiological changes in oestrogens during life and thus puberty, with an increase in oestrogens, has been reported to worsen HAE in 42% to 62% of HAE patients [8, 9]. Besides, the intake of exogenous oestrogens (oral contraceptives, hormone replacement therapy) are well known inducers of HAE worsening [4, 8]. Oestrogens could worsen HAE by activating the contact system, with a subsequent increase in bradykinin release, and an up-regulation of BKB2 receptors [4, 10, 11].

Pregnancy, labour, delivery and breast-feeding in HAE

Pregnancy

A tight follow-up has been advised for female pregnant HAE patients [4, 7, 12]. The physiological increase in oestrogen levels which happens during pregnancy has a well-known role on the worsening of HAE course during this life period [2, 4, 7]. Nevertheless, the influence of pregnancy in HAE is very variable and can improve, aggravate or not produce any change in its course [4, 8, 12, 13]. A summary of the largest published case-series on the management of pregnancy in HAE is provided in Table I [8, 14-19]. A wors-

ening of C1-INH-HAE, as measured by an increase in the number of AE attacks, happens in 38-83% of the pregnancies [8, 15-17]. The early onset of HAE symptoms was associated with more frequent and more severe AE attacks during pregnancy [5, 15]. In addition, age at pregnancy was not found to correlate with HAE severity/activity during pregnancy [14].

C1-INH-HAE activity/severity can also differ from previous to subsequent pregnancies in the same patient [15]. Besides, variability in the number and severity of HAE attacks have been noticed among pregnancy trimesters in some case series [14-16]. Chinniah et al found that HAE activity was higher during the first pregnancy trimester with 6/16 pregnancies having more than 10 AE attacks (versus 3/16 and 0/16 in the second and third trimesters, respectively) [14]. This trend was confirmed by Czaller et al who found a higher percentage of pregnancies with more attacks in the first trimester (49%) compared to the second (37%) and third ones (37%) [15]. This could be explained by the increase in oestrogen levels and the discontinuation of long term prophylaxis (LTP) during the first weeks of pregnancy [4]. On the contrary, Martínez-Saguer et al reported a worsening of symptoms through the two last trimesters, with an increase in the mean number of HAE attacks [16]. In addition, other authors did not observe any difference in HAE activity/severity among the different pregnancy trimesters [17, 19]. Finally, there is a publication in which those patients who had suffered HAE attacks in relation to menstruation were noticed to have an improvement of HAE disease in the third trimester of pregnancy [15].

There are two case-series in which authors analyse if carrying a foetus with HAE has any influence in HAE activity during pregnancy and the results are inconsistent. Whereas Czaller et al found that having a fetus with HAE was associated with a higher frequency of AE episodes during the last trimester of pregnancy [15], Martínez-Saguer et al found no relationship between the foetus having or not HAE and the increase in the number of AE attacks [16].

Machado et al found that the most common triggering factors during pregnancy were emotional stress (65.2%) and trauma (33.3%) [18], in line with previous publications in HAE [20].

Location of HAE attacks during pregnancy has been reported to vary in comparison to pre-pregnant period, with an increase in the frequency of abdominal AE attacks [15-17]. However, Hakl et al did not find a significant difference regarding changes in AE location between pregnancy and one year prior to pregnancy [19]. Mechanical trauma due to

Table I. Pregnancy in C1-INH-HAE patients

	No patients	No pregnancies	No full term pregnancies	Spontaneous abortions	Artificial abortions	Stillbirths	Premature delivery	Cesarean delivery	Vaginal delivery
Bouillet et al 2008	107	227	—	12.7%[1]	—	—	—	12%[2]	88%
Chinniah et al 2009	7	16	16	—	—	0	0	0	100%
Czaller et al 2010	41	118	82/84[3]	25.0%[4]	14.2%	0	9.8%[5]	10%[6]	90%
Martínez-Saguer et al 2010	22	—	35/37[7]	0	—	0	2.9%[8]	51%	49%
González-Quevedo et al 2016	61	143	125	9.8%	2.8%	3	0.7%	12%	88%
Machado et al 2017	13	22	17	5/22 (21.7%)[9]	—	—	0	100%	0%
Hakl et al 2018	6	6	6	0	0	—	0	16.7%	83.3%

[1]10-15% in general French population
[2]16% in general French population
[3]2/82 were twin pregnancies
[4]7.6% in general Hungarian population (n.s.)
[5]8-12% in general Hungarian population, 0% in C1-INH-HAE patients having received pdC1INH
[6]25% in general Hungarian population
[7]2/35 were twin pregnancies
[8]1 of the twin pregnancies (wk 34)
[9]14% in general Brazilian population

the progressive stretching of uterine muscle fibres has been proposed as an explanation for the increase in abdominal attacks [15, 17]. In this line, the patients who referred mechanical trauma as a triggering factor of their AE attacks previously to pregnancy had an increase in the mean of attacks in the three trimesters [15]. Physiological abdominal discomfort during pregnancy could make more difficult the differential diagnosis of an abdominal AE attack. Therefore, abdominal ultrasound could be used to detect signs of abdominal attacks in these patients and also in the follow-up of a treated abdominal attack [14, 15, 17].

Only a few studies publish data on the severity of the AE attacks during pregnancy. Machado et al mention they were usually milder than before pregnancy [18]. González-Quevedo et al described in 2016 a large series of 125 pregnancies in 64 women with C1-INH-HAE with more frequent attacks although they did not find either an increase in their severity [17]. Only one case of life-threatening HAE attack in the 25th week of pregnancy has been published [21].

Abortion

There are few data on the frequency of spontaneous abortion in HAE. The first mention was published by Nielsen et al, who reported that HAE patients with AE symptoms had more frequently spontaneous miscarriage and early delivery [22]. Later, Czaller et al also reported an increased rate of spontaneous abortions (25%) in their case series, but without significant difference with respect to general population [15]. Nevertheless, other authors communicated no increases in spontaneous abortions, early delivery, or stillbirths [8, 16, 17]. It is important to remark that there were no spontaneous abortions in the German case-series in which a high number of patients (18 pregnancies) received individual replacement therapy with pdC1INH [16] and there is a published case report about a patient with multiple spontaneous abortions and a pregnancy that resulted in a healthy new born after LTP with pdC1INH [23].

Although HAE could be considered a reason for artificial abortion in some countries, the frequency of artificial abortion is usually low (2.5%) [17], with the exception of Hungary where it grows up to 14.2% [15]. This can be related to the different laws applying in every country.

Childbirth

Special considerations should be taken into account regarding childbirth. Mechanical trauma involved in vaginal labour could trigger genital and perineal angioedema, but curiously many cases of vaginal deliveries have been reported with no angioedema despite of no prior short term prophylaxis (STP) [4, 15, 17, 18].

Spontaneous vaginal delivery rates are close to 90% of the pregnancies in most series, which is similar to that observed in general population [8, 14, 15, 17]. Nevertheless, there is a study performed in Germany in which caesarean section (abdominal delivery) is much more frequent, close to 50% [16]. However, in this study the rate of primary caesarean sections (23%) was similar to that rate in general population in Germany (25%) [16]. Of note, Machado et al in Brazil reported 100% caesarean sections in their case-series [18], what could be related to the unavailability of specific HAE drugs and the willingness to control when delivery is taking place.

If a caesarean section is being performed epidural anaesthesia is preferred in order to avoid endotracheal trauma and upper airway oedema [4].

Postpartum

Prevalence of postpartum attacks, in particular vulvar and abdominal oedemas is higher and thus patients should be closely monitored in hospital for at least 72 hours after delivery and treatment for acute attacks should be available in case it is necessary [4, 8]. Most of the AE cases after delivery described in the literature are mild even in those cases with no STP before labour [17]. Nonetheless, one death has been reported in a HAE patient who experienced perineal swelling and infection of the episiotomy 48 hours after childbirth [24]. Fatal outcome in this case seems to be more related to septic shock than to a HAE attack [4].

Breast-feeding

The clinical course of HAE during breast-feeding can be aggravated with an increase in the frequency of acute attacks, mainly abdominal [15]. The HAE worsening together with the most frequent abdominal location could be explained by the increase in prolactin levels after labour [25]. This association might also explain the reduction in the frequency of AE attacks after the interruption of breast-feeding and the subsequent decrease in prolactin levels.

Available treatments for HAE and its use during pregnancy, delivery and breast-feeding:

There are currently different classes of drugs used for the treatment of HAE, with different approval status throughout the world. A summary can be seen in Table II.

A. Plasma derived C1-inhibitor concentrate (pdC1INH) obtained by purification of human plasma replenishes the lacking C1-inhibitor and is approved for the treatment of acute AE attacks, short-term prophylaxis and LTP [26, 27]. There are three different products available and with different approval status worldwide: Berinert® (CSL-Behring GmbH, Marburg, Germany), Cinryze® (Shire HGT, Zug, Switzerland) and HAEGARDA® (CSL-Behring GmbH, Marburg, Germany).

B. Attenuated androgens (AAs): 17-α-Alkylated synthetic derivatives (danazol, stanozolol) are very effective in the prevention of acute AE attacks [13, 27]. The exact mechanism of action is unclear, but they significantly increase C1-INH plasma levels and plasma aminopeptidase P, both possibly contributing to their effect [13]. Nevertheless, there are concerns on their safety profile because of the large variety of secondary effects (weight gain, menstrual irregularities, breast atrophy/hypotrophy, acne, voice changes, changes in lipid profile, disorders of libido, impotence, polycythemia, arterial hypertension, hematuria, transient increases in transaminases, hepatic necrosis, cholestatic hepatitis, hepatosplenic peliosis, transient increase in muscle enzymes, rhabdomyolysis, liver adenoma, liver adenocarcinoma) [4, 13].

C. Antifibrinolytics (tranexamic acid): tranexamic acid (TA) inhibits fibrinolysis through a competitive inhibition of plasminogen activation and a subsequent reduction in the conversion of plasminogen into plasmin [13]. It has some protective effect on the frequency of AE attacks in

HAE and is used as LTP mainly in children and childbearing women [13].

D. Recombinant human C1 inhibitor (rhC1INH)(Ruconest®, Pharming Technologies BV, Leiden, The Netherlands): it is produced in transgenic rabbits in which the human *C1INH* gene has been inserted. rhC1INH is excreted into the milk, from which it is purified. It also acts by replacing the lacking C1-inhibitor and is approved for the treatment of acute AE attacks [13, 27, 28].

E. Icatibant acetate (Firazyr®, Shire HGT, Zug, Switzerland), a competitive BK antagonist, acts by selectively blocking BKB2R and is approved for the treatment of acute AE attacks [13, 27, 29].

F. Ecallantide (Kalbitor®, Shire HGT, Zug, Switzerland), an antikallikrein antibody is approved for the treatment of acute AE attacks in the USA [13, 27, 30].

G. Lanadelumab, a monoclonal antikallikrein antibody, is approved for LTP in the USA [31, 32].

H. Virally inactivated fresh frozen plasma (viFFP) could be used as an alternative for LTP, STP and treatment of acute attacks in those countries where specific drugs for HAE are unavailable and if tranexamic acid is contraindicated or ineffective. It replaces C1 inhibitor [4, 12, 13].

No clinical trial has been performed during pregnancy, delivery or breast-feeding in patients with HAE and therefore there is a lack of evidence on the efficacy and safety of the different treatments during these periods and no drug is approved for its use during pregnancy.

Nevertheless, there are recommendations for the use of these drugs, which were formulated in a consensus document [4]. Most of these recommendations were based on case reports, case series and expert consensus.

The current elective treatment for acute HAE attacks, STP and LTP during pregnancy, delivery and lactation is pdC1INH, which has been shown to be safe and effective [4, 12, 15, 16, 33].

Prescribing information for the available pdC1INHs (Berinert®, Cinryze® and HAEGARDA®) says that these drugs should only be given to a pregnant women if clearly needed [34-36] and they have been classified as Category C Pregnancy [37]. Although no controlled study has been performed with pdC1INH during pregnancy or lactation, it has been used in some C1-INH-HAE case-reports and case-series and has been shown to be safe and effective for the treatment of acute attacks, STP and LTP during pregnancy and breast-feeding [14, 15, 33, 38-44]. pdC1INH is therefore recommended as the first-line therapy during pregnancy and lactation in C1-INH-HAE for all these indications [4, 7, 12, 27]. However, there is no experience with the use of HAEGARDA®, a subcutaneous pdC1INH used as LTP at very high doses (60U/kg twice a week) [45].

TA crosses the placental barrier [46], although no significant side effects for the fetus are known and therefore it could be used during pregnancy if pdC1INH is not available [4, 12, 17]. If possible it should be avoided several days before conception, but as its half-life is approximately 2 hours, avoiding it a few days before conception is considered sufficient [4, 12]. The inhibition of the fibrinolytic system raised concerns about the risk of thromboembolism during TA use, but controlled studies did not support it [4, 12, 13]. However, patients with a personal or family medical history of thromboembolic disease might have a higher risk of venous or arterial thrombosis while taking antifibrinolytics and therefore a hypercoagulability study may be necessary before initiating tranexamic acid in this subgroup of patients [4, 12]. Tranexamic acid can pass into breast milk and so it is not recommended during breast-feeding [4].

AAs can cross the placental barrier and produce virilization of the foetus, placental insufficiency and delayed foetal growth [4, 13]. Therefore, AAs should be discontinued at least 1 month prior to conception and be avoided during the whole pregnancy [4, 13]. There is a lack of knowledge on the possibility that AAs are excreted into breast milk and

Table II. Available drugs for HAE and their indications during pregnancy and lactation

Drug	Pregnancy			Lactation		
	LTP	STP	Acute treatment	LTP	STP	Acute treatment
Tranexamic acid	Yes	No	No	No	No	No
AAs	No	No	No	No	No	No
viFFP	(Yes)	(Yes)	(Yes)	(Yes)	(Yes)	(Yes)
IV pdC1INH	Yes	Yes	Yes	Yes	Yes	Yes
SC pdC1INH	(Yes)	No	No	(Yes)	No	No
Icatibant acetate	No	No	No	No	No	Yes*
Ecallantide	No	No	No	No	No	No
rhC1INH	No	No	No	No	No	No
Lanadelumab	No	No	No	No	No	No

No: not indicated; Yes: indicated; (Yes): only indicated if other drugs are not available
AAs: attenuated androgens; viFFP: virally inactivated fresh frozen plasma; pdC1INH: plasma derived C1 inhibitor concentrate; rhC1INH: recombinant human C1 inhibitor
SC: subcutaneous; IV: intravenous
LTP: long term prophylaxis; STP: short term prophylaxis
*Breast-feeding should be avoided 12 hours after icatibant acetate administration

for this reason and the potential side effects in children their use is not recommended during lactation [4].

Pregnancy

Treatment of acute angioedema attacks

Intravenous pdC1INH is the election treatment during pregnancy, labour, delivery, postpartum and breast-feeding [4, 12].

Some case reports have been published in the last years on the use of other therapies during pregnancy. Icatibant acetate has been used in 4 HAE patients for the treatment of some acute AE attacks during 6 pregnancies in the three trimesters [47-50]. The patients gave birth to six healthy children and only one of them was preterm [50]. Icatibant acetate was also used for the treatment of 13 AE attacks in 6 pregnancies in 6 patients and one of the attacks needed a second treatment [19]. The last patients also received rh-C1INH during the pregnancy as described below and gave birth to 6 healthy children [19]. In our practice icatibant acetate is currently advised only in the case of life-threating attacks during pregnancy when pdC1INH is not available or has not been efficacious.

There are two publications about the use of rhC1INH in pregnancy [19, 51]. Moldovan et al used it for the treatment of acute AE attacks in 7 pregnancies [51]. The dose ranged from 2,100 to 4,200 IU and was used for 1 (n=1), 2 (n=2), 6 (n=1), 8 (n=1), 9 (n=1), or 40 (n=1) HAE attacks. rhC1-INH was effective in all attacks and there was no need for additional rescue medication use. All 8 women gave birth at full term to healthy babies and no foetal distress or congenital abnormalities were reported. Hakl et al used rhC1INH for the treatment of 50 AE attacks in 6 pregnancies in 6 patients. The dose used ranged from 2,100U to 4,200U and 4 attacks needed a second dose. Some of these patients also treated some of the AE attacks with icatibant acetate. All the pregnancies came to full-term (one caesarean section and five vaginal delivery) without complications and gave birth to six healthy babies [19].

Long term prophylaxis (LTP)

LTP should be carefully evaluated in each patient by a multidisciplinary medical group with experience in the management of HAE and decided according to the course of the disease.

Intravenous pdC1INH is the election treatment [4, 12, 27]. TA can be used as LTP if pdC1INH is not available [4, 12]. There is no experience with the use of subcutaneous high dose pdC1INH during pregnancy.

rhC1INH was reported to have been used as LTP in one pregnancy within a clinical trial without complications (2 doses 50IU/kg) [51].

Short term prophylaxis (STP)

Patients with HAE can develop upper airway oedema after local trauma induced by medical, dental, and surgical procedures [13, 52]. STP with pdC1INH is usually given 1-6 hours prior to these procedures to prevent the development of AE [27, 53-55].

If there is a need to perform such a procedure during pregnancy, pdC1INH is also the election treatment as STP.

The performance of STP prior to delivery differs within publications. In most publications STP with pdC1INH was occasionally used before uncomplicated vaginal delivery and the patients had mild AE in a very low proportion [8, 14, 17]. Nevertheless, other authors administered STP with pdC1INH prior to all deliveries (vaginal or abdominal) with protection from AE development in all the cases [16, 19]. There is also one series in which STP could not be administered prior to caesarean delivery because of pdC1INH unavailability, but no AE developed during delivery either [18]. The international consensus advises on STP not being needed in spontaneous uncomplicated vaginal delivery, unless the patient is having an increased number of AE attacks during the last trimester or has frequent vulvar AE in relation to mechanical trauma [4]. On the contrary, STP is recommended always in case of instrumental vaginal delivery (forceps, vacuum) or caesarean section [4]. pdC1INH is also the election treatment at the same dose than outside pregnancy [4, 12]. Independently that STP is performed or not prior to childbirth, intravenous pdC1INH should always be available in the delivery room and during hospitalization for on demand use in case an AE attack happens [4, 12, 17]. If there is a need for an emergency procedure during labour or delivery, it should not be delayed because of unavailability of pdC1INH because this treatment can be administered later [4].

Breast-feeding

Although pdC1INH is advised to be used in female HAE patients lactating [4, 27], its breast milk levels have not been measured after exogenous administration in humans [56]. Nevertheless, its levels in breast milk of lactating women taking pdC1INH are expected to be low due to its high molecular weight and any pdC1INH that could be in breast milk is thought to be probably destroyed in the infant's gastrointestinal tract and not absorbed, except perhaps in neonates [56]. There are a few studies with limited information on pdC1INH use during breast-feeding [15, 16, 23, 57]. A total of 26 HAE mothers and their children were healthy after mothers using pdC1INH for the treatment of acute AE attacks during lactation [15, 16, 23, 57].

If icatibant acetate is administered during breast-feeding, lactation should be avoided for the following 12 hours [29].

In summary, HAE is a rare disease with a particular course in female patients. HAE course has a direct relationship with hormone levels, especially oestrogens. Life periods as pregnancy, labour and breast-feeding have variable influence in patients affected with HAE. There have not been clinical trials during pregnancy, delivery and breast-feeding and treatment recommendations are based mostly on publications of case series and expert opinion. Further studies are needed to widen therapy options for female patients with HAE.

Author contributions

All authors contributed toward data analysis, drafting the manuscript, revising it critically for important intellectual content, and gave their final approval of the version to be published.

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MS has received sponsorship for educational purposes from Novartis and Shire and has participated in clinical trials for BioCryst and Shire. RC has received sponsorship for

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