The use of subcutaneous plasma-derived C1 inhibitor in prophylaxis of acute attacks of HAE in pregnant patients

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HAE in pregnancy – summary

HAE I/II – **rarely** presents for the **first time** during pregnancy[1]

nC1INH-HAE more frequently manifests during pregnancy[2,3]

Pregnancy leads to a **hyper-estrogenic status** =
↑ oestrogen exposure → **↑ HAE expression**[4]

Careful evaluation of C1INH testing → physiological transient decline of C1INH concentration even in healthy women (↑ plasma volume?) → re-testing several months after pregnancy[4,5]

Prenatal testing – in case of known mutation responsible for HAE (in mother of father) from chorionic villus, amniotic fluid sample or from the foetal cells from the peripheral blood of the mother[1,4]

HAE = special issue for the management during pregnancy with highly individualised (personalised) approach

Precise diagnosis of HAE in mother before pregnancy is essential

C1INH, C1-esterase inhibitor; HAE, hereditary angioedema; nC1INH-HAE, HAE with normal C1INH.

1. Caballero T, *et al. J Allergy Clin Immunol* 2012;129(2):308–320; 2. Bork K, *et al. J Allergy Clin Immunol* 2009; 124(1):129–134; 3. Cobb G and Bernabe CC. *Cureus* 2023; 15;15(1):e33800; 4. Caballero T, *et al. Int J Wom Health* 2014:6;839–848; 5. Ogston D, *et al. Thromb Res* 1981;23(4–5):453–455.

HAE in pregnancy – severity of attacks

Pregnancy may lead to a **patient's attacks worsening**, **improving** or have **no effect at all**[1–3]

Severity of HAE in various trimesters – inconsistent/**discordant results** and observations[4–7]

There are several **predictors** of more severe disease course (e.g. earlier HAE manifestation in life, mechanical trauma, HAE in foetus???)[4–7]

The most common HAE attacks in pregnancy are **abdominal attacks**[8,9]

HAE, hereditary angioedema.

1. Caballero T, *et al. J Allergy Clin Immunol* 2012;129(2):308–320; 2. Bouillet L, *et al. Am J Obstet Gynecol* 2008;199(5):484.e1–4; 3. Maurer M, *et al. Allergy* 2022;77(7):1961–1990; 4. Bork K, *et al. Am J Med* 2006;119(3):267–274; 5. Park K, *et al. Future Pharmacol* 2023;3(3):586–596; 6. Czaller I, *et al. Eur J Obstet Gynecol Reprod Biol* 2010;152(1):44–49; 7. Martinez-Saguer I, *et al. Am J Obstet Gynecol* 2010;203(2):131.e1–7; 8. Chinniah N, *et al. Aust N Z J Obstet Gynecol* 2009;49(1):2–5; 9. Logan RA and MW Greaves. *J R Soc Med* 1984;77(12):1046–1048.

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HAE in pregnancy – management

Individualised treatment plan for LTP/STP and rescue therapy is **ESSENTIAL**[1,2]

Restrictions for some therapies during pregnancy **(benefits vs. risks)**[1,2]

LTP should be considered for pregnant women with **active HAE**[2,3]

At least **two doses of rescue** therapy (preferentially pdC1INH*)[2,3]

STP before risky events (dental procedures, surgery etc.)[2,3]

Differences regarding therapy restrictions **between pregnancy and breastfeeding**[2–4]

*According to the Summary of Product Characteristics for plasma-derived C1INH products, there is limited data that indicate no increased risk from the use of plasma-derived C1INH in pregnant woman. Plasma-derived C1INH should be given to pregnant women only if clearly indicated.

HAE, hereditary angioedema; LTP, long-term prophylaxis; pdC1INH, plasma-derived C1-esterase inhibitor; STP, short-term prophylaxis.

1. Caballero T, *et al. J Allergy Clin Immunol* 2012;129(2):308–320; 2. Maurer M, *et al. Allergy* 2022;77(7):1961–1990; 3. Park K, *et al. Future Pharmacol* 2023;3(3):586–596; 4. Caballero T, *et al. Int J Wom Health* 2014:6;839–848.

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HAE in pregnancy – guideline recommendations for management

	Rescue	STP	LTP	
pdC1INH* *IV*	YES	YES	YES (if registered)	***Where pdC1INH is unavailable,*** *SDP may be used. Where SDP is unavailable, FFP may be used.*
pdC1INH* *SC*	NO	NO	YES	
rhC1INH *IV*	NO†	NO	NO	
Icatibant *SC*	NO†	NO	NO	
Androgens	NO	NO	NO	
Tranexamic acid	NO	NO	YES	*Second line for LTP with unsure efficacy*
Lanadelumab *SC*	NO	NO	NO	
Berotralstat	NO	NO	NO	
Ecallantide	NO	NO	NO	

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FFP, fresh frozen plasma; IV, intraveneous; LTP, long-term prophylaxis; pdC1INH, plasma-derived C1-esterase inhibitor; rhC1INH, recombinant C1-esterase inhibitor; SC, subcutaneous; SDP, solvent detergent-treated plasma; STP, short-term prophylaxis.

1. Maurer M, *et al. Allergy* 2022;77(7):1961–1990; 2. Hrubiskova K, *et al. Vnitr Lek* 2023;69(4):265–268; 3. Park K, *et al. Future Pharmacol* 2023;3(3):586–596;
4. Caballero T, *et al. Int J Wom Health* 2014:6;839–848; 5. Hakl R, *et al. J Clin Immunol* 2018;38(7):810–815; 6 Moldovan D, *et al. J Allergy Clin Immunol Pract*. 2019;7(8):2938–2940.

Patient case #1

High disease burden
Titrated dose attenuated androgens (LTP)

SERPING1 genetic analysis
Reports a previously undescribed mutation†

2008
17 years old
First clinical symptoms

2015
24 years old
Suspicions of HAE

Typical symptoms:
- Abdominal pain
- Laryngeal attacks
- Peripheral attacks
- **Lowered antigenic /functional C1INH**

2017
Side effects of androgen therapy

Treatment change:
- Tranexamic acid
- Rescue therapy (icatibant and rhC1INH)

2019
First pregnancy

- Patient stops LTP
- Frequent attacks, treated with pdC1INH* IV

Delivery at 41 weeks
HAE negative baby

Tranexamic acid loses efficacy

2021
LTP lanadelumab

Four months therapy with only one attack

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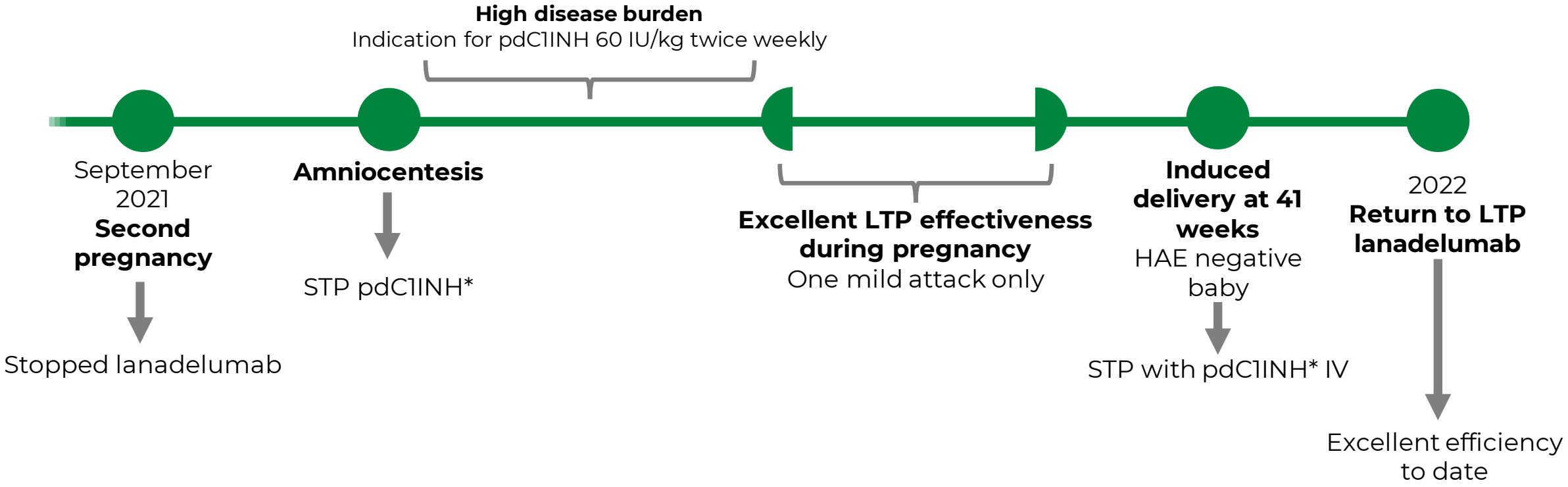
C1INH, C1-esterase inhibitor; (pd)/(rh)C1INH, (plasma-derived)/(recombinant) C1INH; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; SC, subcutaneous.
Hrubiskova K, *et al*. *Vnitr Lek* 2023;69(4):265–268; †Markocsy A., Hrubiskova K, Jesenak M. et al. [submitted]

Patient case #1 (continued)



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Patient case #2

Asymptomatic
until 22 years old
Mother and brother both have HAE

First clinical presentation
at 22 years old

Severe abdominal pain and free peritoneal fluid with genital angioedema after sexual intercourse

First pregnancy
at 26 years old

Delivery at 36 weeks
HAE negative baby

Following two years
No clinical symptoms

Second pregnancy
at 26 years

Examination at 14 weeks of pregnancy due to **high frequency of abdominal attacks** and **asymmetric peripheral angioedema**

Rescue pdC1INH* IV

Indication for LTP
pdC1INH* 3000 IU twice weekly

Excellent efficacy – no HAE symptoms until delivery

Delivery at 39 weeks
HAE negative baby

Present day
No LTP
Rescue therapy only with icatibant

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HAE in pregnancy – take-home messages

- HAE in pregnancy = **special situation**
- **Aim** of management: **full clinical control** over HAE symptoms
- **Personalised management plan** (rescue therapy, STP, LTP)
- **Preferred medication**: **pdC1INH*** IV and/or SC
- **LTP**: **1st line = pdC1INH***, 2nd line = tranexamic acid
- **New treatment options** = **new hope for pregnant women**

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