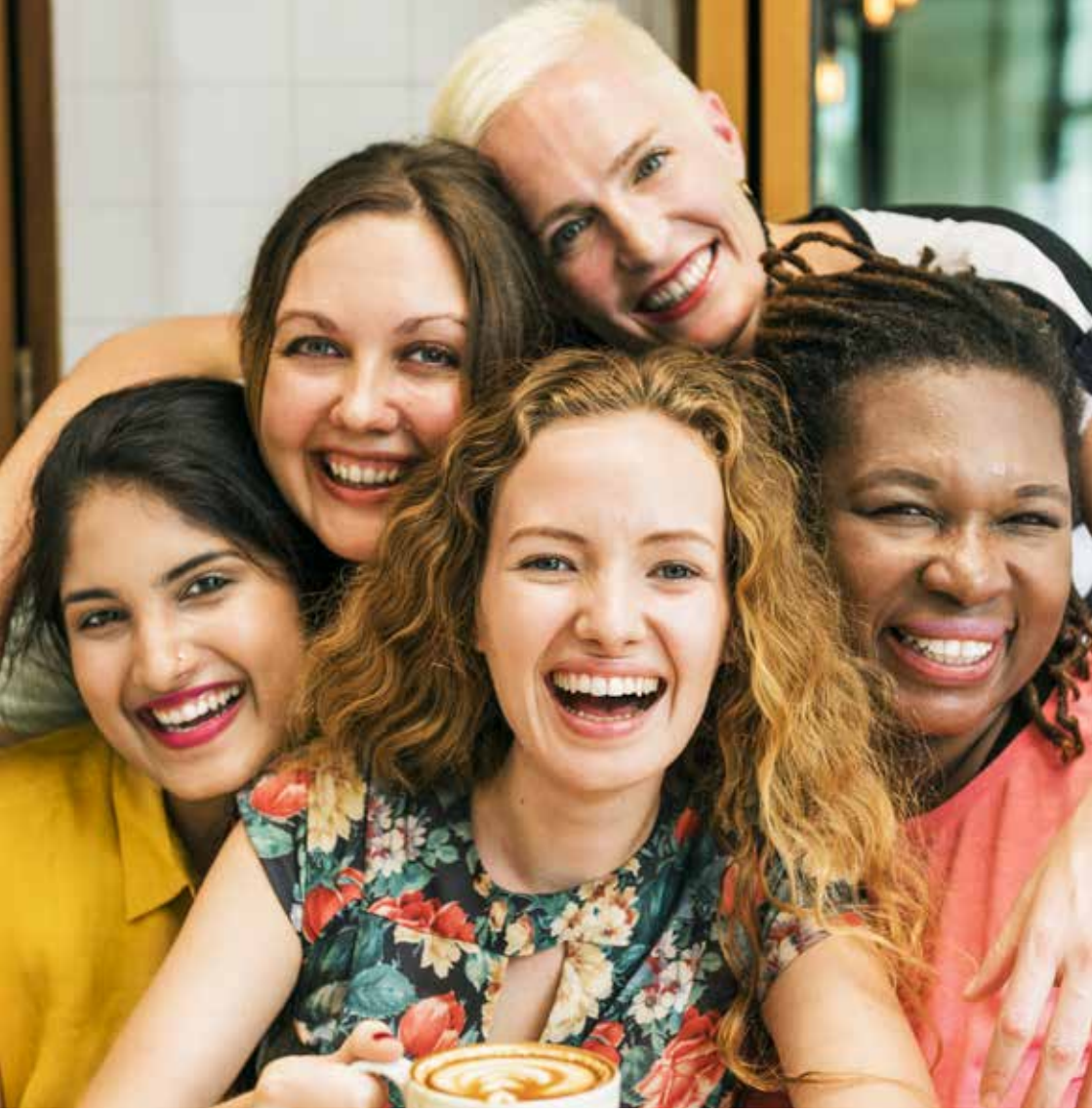


WOMEN WITH HAE

HAEi
HAE International

INDEX

HAEi thanks the US HAEA for their significant contribution to the content of this guide, based on their collaboration with HAE expert physicians.

WOMEN WITH HAE

The purpose of this Guide for Women with Hereditary Angioedema (HAE) is to provide information regarding the unique challenges faced by women with HAE.

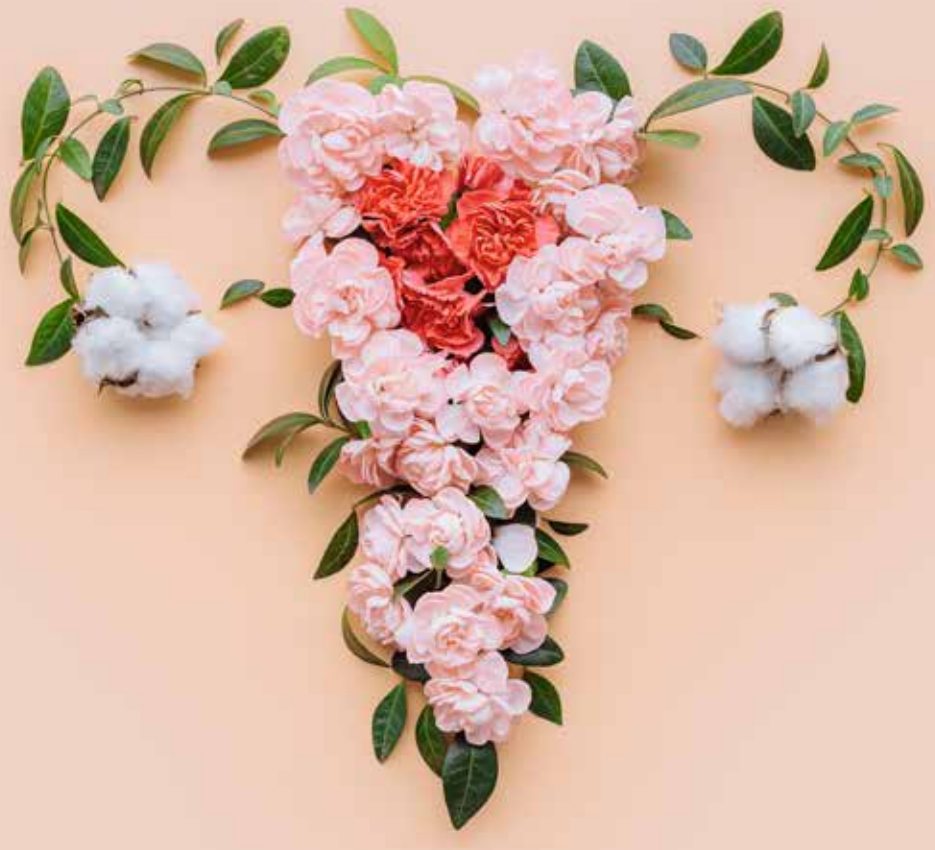
Studies reveal that HAE symptoms are more severe in women than men. This guide is created to help women with HAE navigate three specific life stages:

1) pediatrics and puberty.

2) family planning and pregnancy.

3) menopause and aging.

This guide has been written for an international audience. As a result, with a wide variation in treatments available in different countries, you should always consult your HAE treating physician for options available at every stage of your life.



HAE AND THE FEMALE BODY

Understanding HAE and its effect on the female body

From the onset of puberty to the late stages of menopause, women experience considerable hormonal fluctuations, particularly in estrogen. Changes in estrogen levels can affect the frequency and severity of HAE attacks. As women move through the various life stages, it is important to be mindful of how hormonal variations may impact HAE symptoms and one's approach to treating attacks.

Testing for hereditary angioedema

Early testing is essential to confirm an HAE diagnosis. Blood tests are required to diagnose Type I and Type II HAE.

These blood tests can usually be ordered or undertaken at a physicians office although availability may vary in different countries.

The blood tests required for an HAE diagnoses are:

- C4 Level.
- C1 Esterase Inhibitor Level.
- C1 Esterase Inhibitor Function.

HAE with normal C1-inhibitor

Some people have an HAE diagnosis but have blood tests that return with normal levels of C1-Inhibitor. It is important to discuss this diagnosis with your physician.

Pediatrics through puberty:

CHILDHOOD AND HAE

If you are the parent and/or caregiver of a child with HAE, it is important to be prepared if your child begins to display symptoms. Obtaining an early diagnosis is critical in ensuring that you, your child's doctor or pediatrician, and the HAE treating physician have a comprehensive plan to treat HAE in the event of an attack.

Developing a treatment plan

While many children don't begin to exhibit HAE symptoms until early puberty, it is important to work with your physician to develop a treatment plan, so your family feels confident and prepared if HAE-related swelling does occur.

The treatment plan should include the following, as available in your country:

- A prescription and HAE medication that is available when needed.
- A diagnosis and treatment recommendation letter from your child's HAE treating physician to share with Emergency Department staff.
- A coordinated plan to deal with an attack if the child is at school.

Young children and those without many swelling attacks often cannot identify and recognize HAE swelling. It is important to talk with your child about what to expect if HAE-related swelling occurs.

The age of HAE onset varies considerably from person to person. However, studies show that half of the patients reported the onset of their symptoms by age ten, and most people experienced their first attack before 18. There also seems to be an increased frequency of attacks during puberty or adolescence and the arrival of menstruation (which leads to changes in estrogen levels).

Advocate

As a parent and/or caregiver, you will be your child's best advocate. Therefore, it is important that you (1) understand how HAE can affect your child's life and (2) can speak knowledgeably on your child's behalf. For more information on the various types of angioedema, symptoms, triggers, and current treatments, please visit the HAEi website at haei.org.

Create a treatment plan

Parents and/or caregivers should work with their child's physician to create a plan to manage HAE swelling attacks, including treatment where available.

Set up an emergency plan

It is important that everyone involved in your child's care knows your plan for an HAE emergency. Prepare and provide detailed information with everything needed to take care of your child in an HAE emergency, including your child's current therapy, your wishes for how and where your child should receive treatment, and your best contact information.

HAEi has developed emergency cards containing clear and straightforward information about HAE and the treatment required during an attack. Emergency cards in many languages are available through our HAE Companion app and on the HAEi website at haei.org.

If you're traveling with your child, make sure you know where the nearest emergency medical facility is located. Using HAEi's app, HAE Companion, you can always find the nearest HAE-knowledgeable physician or hospital.

Frequently asked questions answered by our HAE expert physicians:

FROM A CHILD'S OR TEENAGER'S PERSPECTIVE

What adults might I need to talk to about my HAE?

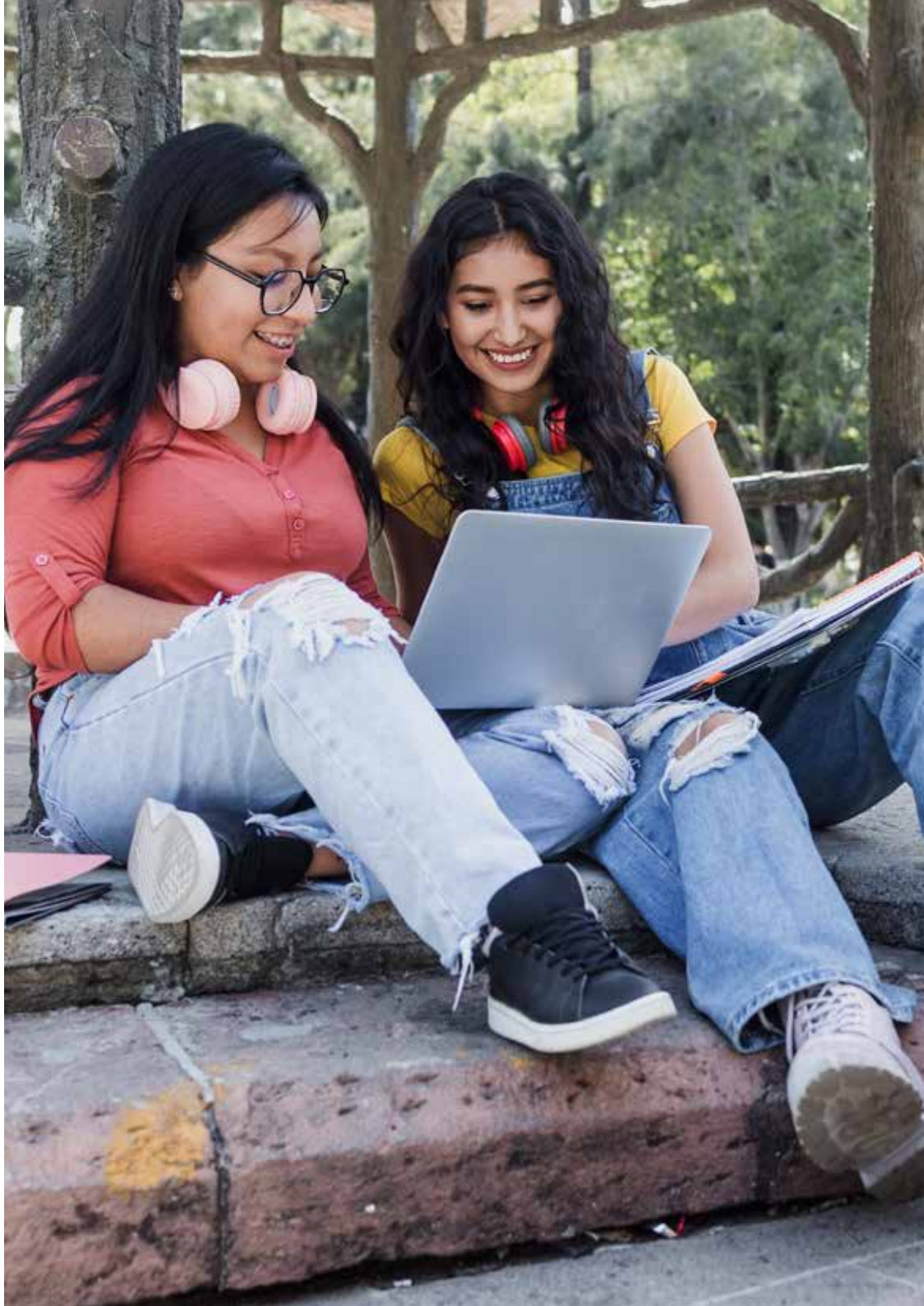
Talking to adults about your HAE is important. Adults in your life are in a position to support you if you have an attack and need help. These adults might be your school's teachers, nurses, coaches, and counselors. Other adults to speak to might be a Girl Scout troop leader, your friends' parents, adults who run after-school programs, and anyone with whom you have regular contact. Talking to them about your HAE helps them be prepared to support you if you have an HAE attack.

What are some tips to help monitor my HAE so I can track attacks and triggers?

Keeping track of when attacks occur, where on the body you swell, and possible triggers can help you better understand your HAE attacks. You can keep a journal or use HAEi's free and easy-to-use electronic diary, the **HAE TrackR** app, to monitor and document your attacks. You can also keep a journal of your menstrual cycles and see if they correlate with attacks and not feeling your best. Share that information with your HAE physician when you next have an appointment, as it may be very important.

How might puberty and menstruation affect HAE symptoms, and what should I expect during this time?

Hormones can play a role in the symptoms and severity of HAE. Puberty often causes increased (or first) symptoms of swelling to occur. Puberty comes with many changes. It is important to embrace the changes and challenges during the transition to adulthood. Menstruation may lead to more frequent and severe attacks in women. If this becomes difficult and greatly impacts your quality of life, you should discuss it with your physician.



Is genital swelling common?

The location of swells on the body can be different for everyone. Some people never experience genital swelling, while others experience swelling in this area more frequently. Genital swelling can be the first sign of HAE for some people. This can be scrotal swelling for boys and labial swelling for girls. It is often due to trauma to the area (i.e., riding a bicycle) but can occur without trauma.

How can I explain HAE to my friends?

Some people with HAE say they have special blood. Educating your friends will make everyone understand and help you on your journey.

How should I manage HAE and extracurricular/physical activities?

Be active and live life to the fullest. Talk to your physician about developing a plan to maximize your activities safely and progressively. An active and healthy lifestyle approach can help your overall mental and physical well-being.

Frequently asked questions answered by our HAE expert physicians:

FROM A PARENT OR ADULT FEMALE PERSPECTIVE

What should an emergency plan look like for my child? What should I prepare in advance with my child's physician?

Make sure you have the medical records that include diagnosis, blood test results, and contact information for your child's HAE specialist printed and/or stored on a USB or memory stick. Have a telephone number for your child's HAE specialist so they can speak to emergency and other hospital staff if your child was taken to an emergency department that doesn't know about HAE. Ensure that you and your child frequently follow up with the HAE treating physician to be sure the most appropriate therapy is in place, considering any additions to treatment in your country.

HAE and birth control - what do I need to know? What kind of birth control options should I discuss with my doctor?

Speak to your physician about the birth control method you plan on using. For many patients, estrogen-based hormones can increase the rate and severity of HAE swelling attacks.

Is there a connection between urinary tract infections and HAE?

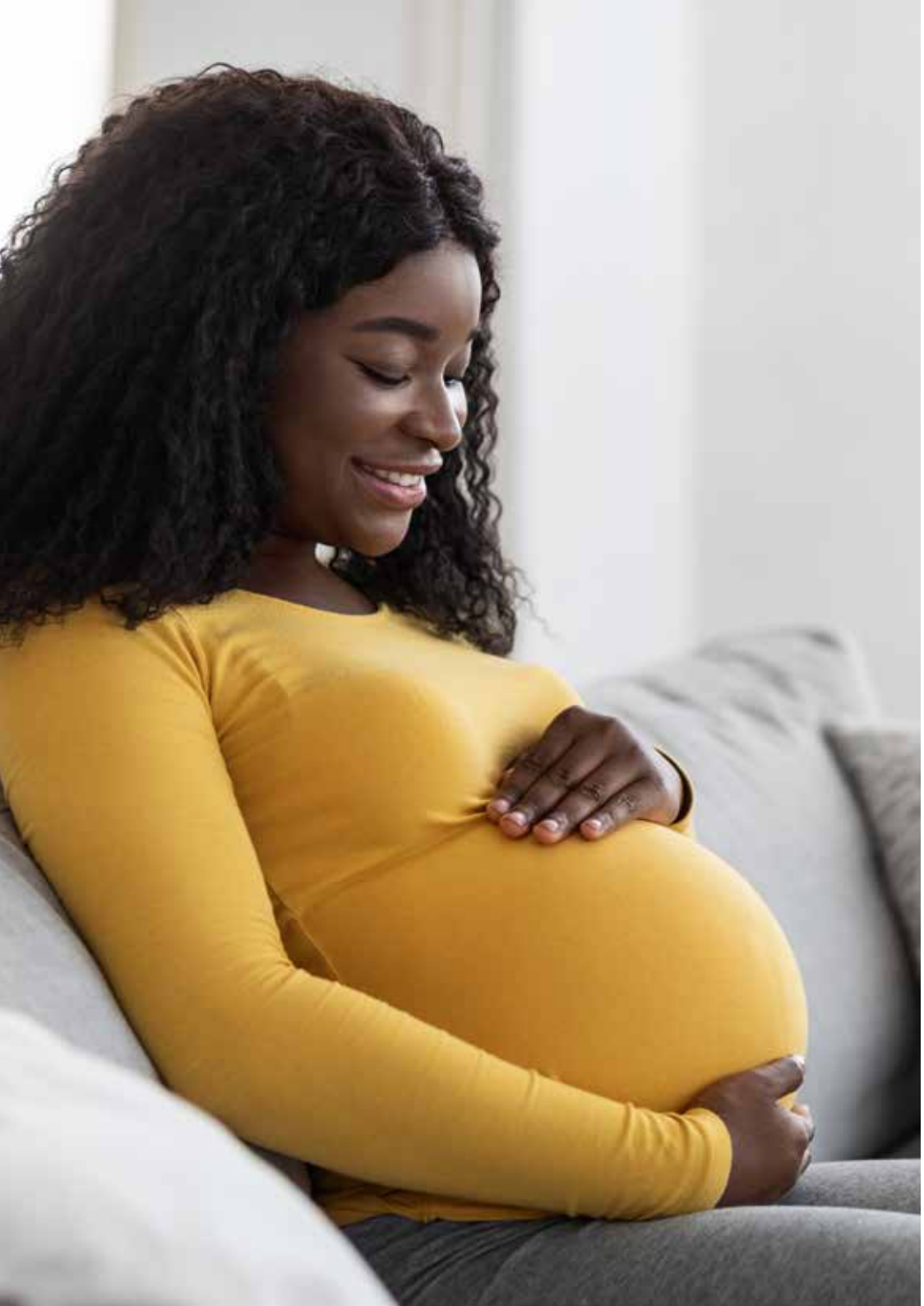
As with any infection or inflammation, these can trigger HAE attacks.

How can I ask my physician about a new HAE treatment?

Discuss upcoming therapies and see if your current treatment plan works for you. This is why regular visits and follow-ups with your physician can be helpful, if not life-changing. Open and frequent communication between you and your physician is as important as ever. Remember that your HAE attacks and triggers in life may change from month to month or year to year.

Do you have any stress management tips?

Introduce nature and natural means of stress management. This can include anything from a hike to a walk by the water (river/ocean) or low-impact mindful activities such as meditation, music, and other methods that promote deep relaxation.



PREGNANCY AND FAMILY PLANNING WITH HAE

Planning to have a family and going through pregnancy is an exciting time in life. HAE does not impair fertility, but for women with HAE, it is important to understand how the condition could affect their pregnancy. Developing a plan and working with your obstetrician and/or gynecologist and HAE-treating physician will establish the basis for a healthier and happier pregnancy.

Just like the symptoms of HAE, each pregnancy experience can be different.

Communication is key

Talk to your HAE treating physician, as well as your obstetrician and/or gynecologist, about establishing an HAE treatment plan. Ensure ongoing and open communication between your HAE treating physician and obstetrician and/or gynecologist.

Genetic implications

HAE is an inherited condition, and each baby born to a parent with HAE has a 50 percent chance of inheriting the disease. If you want to get pregnant or are pregnant, your doctor will follow you closely to discuss the appropriate management of your HAE with you.

Fertility therapies

Couples struggling to conceive might be considering fertility treatment options. Treatment-related fluctuations in the female hormone estrogen can influence HAE symptoms. It is important that women choosing to pursue fertility treatments discuss whether changes may be needed to their current HAE treatment plan.

During pregnancy

Like HAE, no two pregnancy experiences are the same, and HAE attacks can fluctuate in frequency or severity during pregnancy. Your HAE treating physician can help you develop a treatment plan specific to your needs before, during, and after giving birth and while breastfeeding.

International guidelines (2021) state that treatment with anabolic androgens (or steriods) is not recommended during pregnancy and breastfeeding. Tranexamic acid may be considered and plasma derived C1-INH is recommended as a preferred therapy for pregnant or breastfeeding HAE-1/2 patients. Solvent-detergent treated plasma (SDP) may be used when C1-INH is not available and fresh frozen plasma when SDP is not available. Other medications, at the time of the guidelines publication, do not have published data in pregnancy and breastfeeding.

Be prepared for HAE symptoms

While some women do not experience any HAE attacks while pregnant, others report increased frequency and/or severity during this hormonal change. It is important to pay attention to the early signs of HAE symptoms so you can quickly administer treatment and limit the severity of an attack as soon as the swelling is recognized. Remember that treatment with anabolic steroids (also known as androgens) is not recommended during pregnancy.

Secure your medications

If you have an acute HAE treatment that is recommended for use in pregnancy, ensure that it is available at the hospital where you plan to have your baby. You should also secure any additional treatments you may need (acute and prophylactic) after having your baby and when you are discharged.

Postpartum considerations

- Keep medications handy

  HAE attacks are rare when having your baby, but there is some indication that an increase in frequency and severity of attacks is possible postpartum. Ensure you have enough medication in the weeks and months following delivery while your body is undergoing hormonal changes.

- Breastfeeding

  Breastfeeding may be associated with an increased number of maternal attacks, but is recommended based on benefits provided to the infant. There are effective HAE treatments which can safely be used while breastfeeding. Androgens should not be used during breastfeeding. If you are considering breastfeeding your child, speak to your physician about available options that may be right for you.

- Testing your child for HAE

  While you may be eager to learn whether your child also has HAE, it is generally recommended that you wait until your baby is at least one (1) year old to test for HAE to ensure a more accurate test result.

Frequently asked questions answered by our HAE expert physicians:

FROM A PREGNANT WOMAN'S PERSPECTIVE

What medications would I want to use to treat my HAE while pregnant?

While there have been no clinical trials to test the safety of HAE medications on pregnant women and their babies, there is a long history of pregnant women in the US and Europe who have used plasma-derived C1-Inhibitor replacement therapies during pregnancy. International guidelines recommend plasma-derived C1 inhibitor as the preferred therapy during pregnancy and breastfeeding. However, this is not available in all countries. See previous page for more information from the guidelines. You should speak with your HAE physician to determine which therapy would be best for you.

Medications to specifically avoid during pregnancy include all forms of androgens, which are relatives of the male hormone testosterone. These medications could affect fetal development and should be avoided if you are planning to have a baby, and should be stopped immediately if you discover that you are pregnant.

Does having HAE classify my pregnancy as "high risk"?

It is usually the obstetrician and/or gynecologist and their team who decide whether or not a pregnancy is considered high-risk. Obstetricians and/or gynecologists, however, will often classify patients with HAE as 'high risk' due to the extra considerations that need to be addressed during pregnancy. This is nothing to feel alarmed about. It just means that healthcare professionals pay special attention to you and your baby to ensure a complication-free delivery.

What if I need to have an unexpected cesarean section?

International guidelines recommend the use of a C1-Inhibitor intravenous injection, where available, before having a cesarean. This is to ensure that your C1-Inhibitor levels are high enough to protect you from HAE swelling. It is also important to have several doses of medication on hand if swelling occurs after the surgery. This question also highlights the importance of discussing plans in advance with your obstetrician and/or gynecologist and HAE specialists, so you are confident that everyone will be prepared.

Will being pregnant affect my HAE symptoms?

Research has shown no way to predict how your HAE symptoms might change during pregnancy. It is possible that your symptoms could get better, they could get worse, or they could stay the same. Adjustments to your medications can be made if your pregnancy causes changes in your HAE symptoms.

Does the gender of the baby influence the severity of HAE while pregnant?

There is no evidence to suggest that the baby's gender will impact the frequency and severity of HAE symptoms.

I've already had one child, and I am pregnant with my second. Can I expect my HAE symptoms to be similar to my first pregnancy?

It has been widely reported that each pregnancy experience is different. While someone may have little to no change in their attack frequency during their first pregnancy, there can be variation in the frequency and severity of symptoms during subsequent pregnancies.

Frequently asked questions answered by our HAE expert physicians:

What should I expect and prepare for during the delivery of my child?

The majority of women report that everything goes quite well during delivery. As noted earlier, it is important to have several doses of medication on hand if HAE-related swelling occurs. After having your baby, it is also important to be aware that women with HAE could have increased HAE attacks.

What is the chance of passing HAE on to my child?

If either parent has HAE Type I or Type II (C1-Inhibitor deficiency), there is a 50 percent chance of the condition being passed to their child.

Scientists suspect that the inheritance pattern for HAE with Normal C1-Inhibitor is similar to what is seen in HAE Types I and II, but research is ongoing.

At what age is it recommended to have my child tested for HAE?

It is recommended that all children in your family be tested for HAE as early as the first year of life. It is important to know whether your child has HAE so you can be prepared in the event of an attack. For HAE-C1-INH (Type I & Type II), this involves simple blood tests and can usually be ordered or undertaken at a physician's office, measuring levels of C4, C1-Inhibitor (quantitative), and C1-Inhibitor (functional). There is currently little information regarding testing children for HAE with Normal C1-INH.

How do I talk about HAE with my obstetrician and/or gynecologist?

It is important that you establish a communications pathway between your HAE-treating physician and obstetrician and/or gynecologist. Doing so will ensure that questions are answered and that the physicians work together to create a treatment plan for you.

Your treatment plan should:

- Ensure everyone is aware of medication administration procedures and that the medication is available at all times,
- Address how the person with HAE will access medication while in the care of the hospital (will it be brought with them, or will they need to use the pharmacy at the hospital?), and
- Confirm there is a plan in case a cesarean section is performed (ask any questions that the anesthesiologist might have).

What should I expect after having my baby?

Recovery from either a vaginal or cesarean section delivery could trigger HAE symptoms, so it is important to treat any swelling suspected to be HAE-related at the onset. As we discussed, while the actual birth usually goes well, it is during postpartum that many women might have increased issues with HAE symptoms.

Should I expect any changes in my HAE while breastfeeding?

This is another area where we need more information. While not common, some women have indicated they have experienced more HAE symptoms during breastfeeding. Please discuss your treatment with your HAE physician, if you decide to breastfeed. If you have C1-INH-derived therapies, it is recommended that you continue with these to treat or prevent HAE attacks while breastfeeding.

Resources for:

FAMILY PLANNING AND PREGNANCY

Coordination care for pregnant woman with HAE

Below you will find suggestions for planning throughout your pregnancy. Talk with your obstetrician and/or gynecologist about having a treatment available where you are to deliver.

My pregnancy journal

Track your pregnancy experience. Note your water intake, attack frequency, and any changes you notice throughout your pregnancy and postpartum experience.

My pregnancy checklist

- Inform your obstetrician and/or gynecologist that you have HAE.
- Establish communications between your healthcare team (HAE treating physician and obstetrician and/or gynecologist).
- Work with your healthcare team to create a treatment plan that covers all aspects of your pregnancy, including HAE treatments for emergencies and any symptoms occurring at the hospital.
- Use HAEi's free and easy-to-use electronic diary, the **HAE TrackR** app, to keep track of your HAE symptoms.

Second trimester (preparing for delivery)

- Obtain a letter from your HAE treating physician or obstetrician and/or gynecologist noting treatment procedures in the event of a cesarean or other necessary procedures.

Third trimester

- Have a printed letter outlining the treatment plan with the contact information of both the obstetrician and/or gynecologist and the HAE treating physician.

Take control of your HAE with **HAE TrackR**

HAE TrackR is developed by fellow HAE patients at HAEi and designed to record your HAE attacks, treatments, and the impact HAE has on your life and the life of your loved ones. The app can be used to make important decisions on how best to manage your HAE; for example, you can share a report of your attacks and treatments with your physician if you choose to.

HAE TrackR can be accessed from any device (smartphone, tablet, or computer) anywhere in the world – visit haetrackr.org to learn more and start using the app.

Frequently asked questions answered by our HAE expert physicians:

MENOPAUSE AND AGING

Menopause typically results in decreased estrogen production, significantly affecting a woman's HAE symptoms. Physicians often prescribe estrogen replacement therapy for menopausal women. It is important to discuss the risks and benefits of hormone replacement with your HAE-treating physician.

I'm approaching the age of menopause. How might this affect my HAE?

Studies investigating the effect of menopause on HAE symptoms have shown mixed results. One large published study showed that following menopause, HAE symptoms improved in 13% of women, remained the same in 55%, and worsened in 32%. Another large HAE center has reported experience that after menopause, 50% of women improved, but 15% worsened, in some cases with severe symptoms. HAE is highly variable and unpredictable during menopause. Therefore, it's important to follow up with your HAE-treating physician to ensure your HAE management plan is the best it can be.

Can I use hormone replacement therapy during menopause?

Systemic (oral or injected) medications containing estrogen are known to increase angioedema symptoms in most women (up to 80%) with HAE. The effect of topical estrogen-containing medications (patches or lotions) on HAE has not been studied in detail. However, extreme caution should be taken with any estrogen-containing medication. Avoiding estrogen treatments is generally recommended during menopause, and other non-estrogen treatments or strategies are encouraged to treat symptoms of menopause.

Frequently asked questions answered by our HAE expert physicians:

Can I take hormone replacement therapy if I'm on an HAE preventive treatment?

The answer to this question is unknown because this topic has not been adequately studied. Estrogen-containing medications are known to increase the frequency of HAE attacks. Therefore, extreme caution should be taken if estrogen treatment is introduced.

What can I do to help with menopause symptoms if I cannot take estrogen replacement?

Treatment options for symptoms associated with menopause should be carefully discussed with your gynecologist or primary care physician and HAE-treating physician. As noted earlier, estrogen medications are generally best avoided. The data on transdermal or topical estrogens is less clear, with a few reports of these formulations being tolerated in some women with HAE but worsening symptoms in others. While certain women may tolerate transdermal or topical estrogen treatment, these should be undertaken with extreme caution. Progestin-only medications (without estrogen) are beneficial for some menopausal symptoms and can sometimes have a preventative effect on HAE symptoms. Non-hormonal medications have also shown benefit in managing symptoms of menopause. These include selective serotonin reuptake inhibitors (SSRIs) such as paroxetine or citalopram, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, desvenlafaxine, gabapentin, clonidine, and oxybutynin. Because of the numerous options, it is important to discuss the treatment of menopausal symptoms in detail with your healthcare team.

What can I expect if I have to get a hysterectomy?

There are two primary HAE-specific issues to consider with a hysterectomy. The first is the risk of the surgical procedure triggering an HAE attack, as this can occur with surgical trauma or manipulation of the airway if general anesthesia is used. The surgical and anesthesia team should be aware of the HAE diagnosis and have a management plan for HAE in collaboration with your HAE-treating physician. The second issue relates to any long-term hormonal effects of the surgery. This depends on whether the ovaries are removed (oophorectomy) simultaneously with the uterus (hysterectomy). The decision to remove the ovaries is important to discuss with your gynecologist/surgeon, as there are potential long-term health risks and benefits. Removal of the ovaries will essentially cause menopause by reducing estrogen production. While this may influence HAE symptoms, the clinical effect is unpredictable and unreliable. Hysterectomy/oophorectomy is not currently recommended as a treatment approach for HAE, and these procedures should only be done for other medical reasons.

Should I change/decrease my C1-INH replacement if the symptoms decrease during menopause?

Adjustment of any HAE medications, including C1-INH replacement, should be discussed and made in collaboration with your HAE-treating physician. Such changes are generally based on the clinical course of HAE symptoms, the quality of life factors, and potential adverse effects of the medication. Often, adjustments to treatment are important during different life phases or events, particularly with long-term prophylactic regimens. Menopause is a time when HAE symptoms may improve or worsen due to the influence of hormonal changes, so it may be very reasonable to consider adjustments to the treatment plan. Make sure to discuss this with your HAE-treating physician to ensure this is done as safely as possible.

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