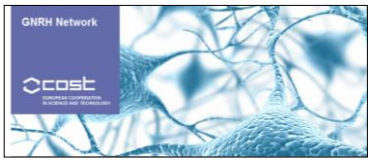


cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

English

What you should know about congenital hypogonadotropic hypogonadism (CHH) & Kallmann syndrome (KS)

What is CHH?

CHH is caused by a **deficiency of GnRH (gonadotropin releasing hormone)**. When combined with a lack of sense of smell (anosmia), it is known as Kallmann syndrome (KS). CHH and Kallmann syndrome are diagnosed and treated the same way.

What does GnRH do?

GnRH is an essential hormone for sexual development, puberty and fertility.

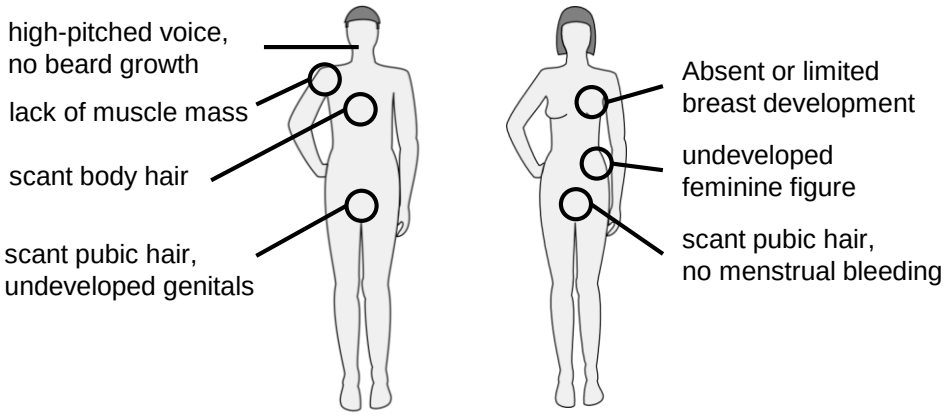
1. GnRH is released from the the hypothalamus, an area of the brain that controls several body functions.
2. GnRH acts directly on the pituitary gland (a nearby pea-sized gland in the brain) to release two hormones: luteinising hormone (LH) & follicle stimulating hormone (FSH).
3. LH & FSH are important for puberty and fertility
   - in men: LH & FSH stimulate the testes to make testosterone and sperm
   - in women: LH & FSH stimulate the ovaries to make oestrogen and progesterone that are important for fertility

What happens if there is no GnRH?

Complete or partial GnRH deficiency results in absent or very low LH and FSH. This results in **failure of puberty and infertility** (see figure below). This means that:

- in men: 1) the testes do not grow, 2) testosterone is not produced in normal amounts and 3) sperm does not develop.
- in women: 1) although eggs are present, they do not develop or grow and are not released (ovulation), 2) oestrogen and progesterone are not produced, and 3) no menstrual periods (bleeding) occur.

Signs of failed puberty in adolescents and young adults



These problems are almost always present at birth (called congenital). However, the diagnosis is often made in teenage years or early adulthood when puberty does not start. **Importantly, this condition is treatable. In most cases it requires life-long hormone replacement & ongoing care.**

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Who is affected by CHH?

Both men and women are affected. CHH is more often diagnosed in men. The reason for this is not clear. It may be that many affected women see a gynaecologist and given a prescription for the contraceptive « pill » to have regular periods, yet they may not get a clear diagnosis. Some patients never get an exact diagnosis and may never see a specialist for GnRH deficiency.

How many people are affected?

CHH is rare so an accurate estimate is difficult. We believe CHH occurs in about 1 in 4,000 to 10,000 people. This means that the entire number of patients with CHH in Europe (around 74,000) would fill the Olympic stadium in Berlin Germany.

Is CHH inherited? CHH can be hereditary. This means it **can be passed down** through the generations and within families. In many cases, there is no apparent family history. A genetic cause can be identified about half (50%) of the time. Research is ongoing and there is more to discover about the genetic causes of CHH. In most cases, it is difficult for healthcare providers to reliably and accurately predict if a patient will pass CHH on to their children.

Half of patients have a known genetic cause, half have no known genetic cause

CHH is complicated because in some cases CHH can be caused by the combination of two or more changes (mutations) in different genes. This makes it **challenging to predict if the CHH will be passed on to children**. For one gene, *ANOS1* (*KAL1*) , it is simple to predict. More research is needed to better understand this and improve diagnosis.

How is CHH diagnosed?

CHH is difficult to diagnose. There is a wide range in the normal timing of puberty. This makes it very difficult to decide if puberty is delayed (but normal), or if it is CHH and needs medical treatment. Regular appointments are needed to follow the progress of puberty. Patients should always be asked about a defective sense of smell. Signs pointing to CHH are:

• **boys -** no signs of puberty by age 16 with low testosterone, LH & FSH.

• **girls -** no breast development by age 14-15 and no menstrual period (bleeding) by age 16-17 with low oestrogen, LH & FSH.

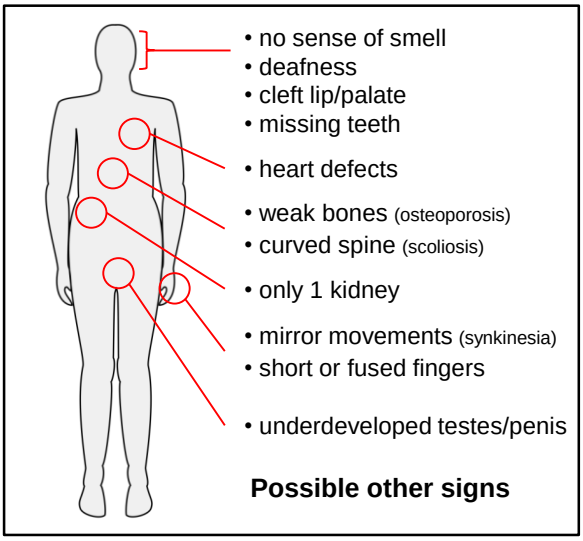
• **Other tests must be done** to make sure there are no other problems causing the low hormone levels. Tests include blood tests and imaging studies (X-rays, ultrasound & MRI)

Are there early signs to look for?
For many people there are no signs of CHH before the failure of puberty.

Some male infants may show signs suggesting CHH, **micropenis or undescended testes** (cryptorchidism).

Micropenis can be treated in infancy / childhood with hormone treatment. Undescended testes should be corrected by surgery early in the first year of life to help future fertility.

There are other signs linked with CHH that happen in some but not all patients.



How would the absence of puberty affect somebody?
Not going through puberty at the same time as peers **can be very stressful and sometimes traumatic**. This can be a major problem for some patients with CHH. The impact can be severe in some cases though it will vary from person to person. The teenage years can be difficult for teenagers who enter puberty at the normal time, but not going through puberty and being left behind by the peer group may result in potential issues including:

- low self-esteem, little confidence
- shyness, difficulty interacting with peers
- anxiety, depression
- poor body image

An abnormal sense of smell can effect your sense of taste and enjoying food. People may not be able to detect gas (or when foods spoil). Some may be concerned about body odor.

What can you do?
On the whole, these can be overcome. Psychological counselling and therapy can be useful.

1. **talk with your healthcare provider** - they may not realise that you are having a hard time. They can help you find counselling and support.
2. **connect with other patients -** using online groups (Facebook, RareConnect.org) and face-to-face support groups can be very helpful. These are places where patients can talk about issues that are important to them. Other patients understand what it is like to live with CHH day-to-day and can provide practical advice and support.

What should you do to be healthy?
Having CHH should not shorten your life. There are things that you can do to stay healthy

- have ongoing healthcare and visits
- take your treatment as prescribed
- eating a healthy diet
- get regular exercise
- don't smoke tobacco

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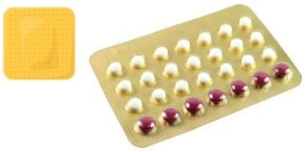
Is CHH curable?

Currently, **there is no cure for CHH**. It is very difficult to cure a congenital (genetic) disorder. Research is ongoing to see if we can restore GnRH production from the hypothalamus. This research is still in a very early stage but it is hoped that this will be possible in the future.

Are there treatments available for CHH?

Treatments are available to develop the outward signs of puberty - such as beard growth for men and breast development in women. Special hormone treatments also available to help develop fertility in most cases.

men: **Testosterone** (gel applied to the skin or injections) is the most common treatment to develop signs of puberty. Treatment induces growth, deepening of the voice, beard growth, penis growth, sex drive (libido) and sexual function – but not fertility.

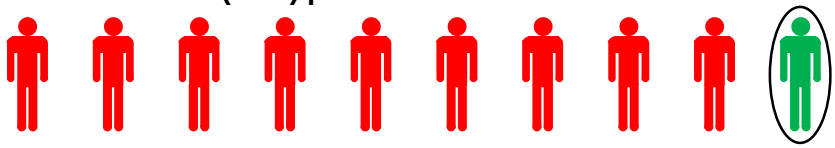


women: low dose oestrogen (patch or pills) induces growth and helps develop breasts, sex drive (libido) and a feminine figure, combined with progesterone this causes regular menstrual periods (bleeding) – but not fertility.

When treatment is first started, the **dose adjustment is gradual**. This can be frustrating for some people who might expect rapid results. However, it is important to maximise growth (and breast development in females)

A few people with CHH recover after treatment and can produce normal hormone levels. This is called a reversal. The reasons for this are not understood and we are unable to predict who will have such a reversal. **This recovery does not always last. So, it is important to be followed closely by a healthcare provider.**

About 1 in 10 (10%) patients with CHH have a reversal

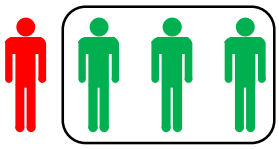


Can a person with CHH become fertile?

Yes, **CHH is a treatable form of infertility.** The majority - but not all - people with CHH can become fertile with **specialised hormone treatment.**

- specialised treatment can be either hormone injections several times a week or wearing a portable GnRH pump (like the pump used for diabetes).
- fertility treatment requires care from experienced specialists (**reproductive endocrinologists**)
- sometimes (but not always) assisted fertility is needed, such as *in vitro* fertilisation (IVF).

Fertility: Overall, 3 out of 4 patients (75%) are successful



Men: it can take up to 2 years to develop sperm

Women: in some cases, fertility is achieved in a few months

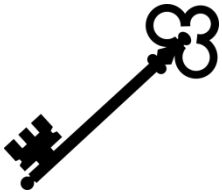
Are there any risks if CHH is not treated?
While testosterone and oestrogen are not vital hormones for life, their absence (or deficiency) can seriously impact **health, sexual function and quality of life.**

In men & women

- increased risk for **low bone density (osteoporosis)** – this means that the bones are weak and there is a higher than normal risk for fractures. If CHH is not treated, osteopeorosis can affect a person at any age. Some people with CHH need extra treatment for osteoporosis.
- **decreased sexual function and desire** is a result of low hormone levels
- **fatigue, feeling down, and depression** are common among patients off treatment

Men without treatment are also at higher risk of having metabolic problems such as getting pre-diabetes or diabetes. **These risks can be decreased by staying on treatment**.

Key Points:



- CHH is rare condition caused by GnRH deficiency
- CHH results in absent puberty and infertility
- CHH should not shorten your life
- CHH is difficult to diagnose
- many people are not diagnosed until late in teenage years or early adulthood
- unlike many rare diseases, there are treatments available
- you need life long treatment and regular visits with your doctor
- talk with your doctor about treatment options to decide what is best for you
- stopping treatment has negative consequences on your health and wellbeing
- fertility is possible in most cases with special hormone treatment
- you can pass CHH to your children, so genetic counselling is recommended
- CHH is psychologically difficult for some people
- you can find support from your healthcare providers and patient groups

Helpful reference
http://www.nature.com/nrendo/journal/v11/n9/full/nrendo.2015.112.html

Helpful websites
http://www.gnrhnetwork.eu/hhn_home/hhn-patients_familles_gnrh_deficiency_kallmann_syndrome/hhn-onlinesupportgroups.htm

https://www.rareconnect.org/en/community/kallmann-syndrome

https://www.facebook.com/KallmannSyndrome/

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