KALLMANN SYNDROME

Hypogonadotropic Hypogonadism (HH), Ks, Anosmic Hypogonadism, Anosmic Idiopathic Hypogonadotropic Hypogonadism, Hypogonadism With Anosmia, Hypogonadotropic Hypogonadism-Anosmia Syndrome

A genetic condition where the primary symptom is a failure to start puberty or a failure to fully complete puberty.

Diagnosis: Q Male & Female

Related Diagnoses:
Erectile dysfunction | Undescended testes | Non-obstructive azoospermia | Hypogonadism | Amenorrhoea

About Kallmann syndrome

Kallmann syndrome is a condition characterized by delayed or absent puberty and an disturbed sense of smell. KS is a part of a group of conditions that come under the term hypogonadotropic hypogonadism (HH), which is a condition in which the male testes or the female ovaries produce little or no sex hormones.

The features of Kallmann Syndrome and hypogonadotropic hypogonadism (HH) can be split into two different categories; “reproductive” and “non-reproductive”. Not all symptoms will appear in every case of KS/HH, not even amongst family members. However if a boy or girl has not started puberty by either 14 (girls) or 15 (boys) and they have one of the non-reproductive features then a referral to reproductive endocrinologist might be advisable.

Hypogonadism can occur through a number of different ways. The use of the term hypogonadotropic relates to the fact that the hypogonadism found in HH is caused by a disruption in the production of the gonadotropin hormones normally released by the anterior pituitary gland known as luteinising hormone (LH) and follicle stimulating hormone (FSH). LH and FSH have a direct action on the ovaries in women and testes in men. The absence of LH and FSH means that initially puberty will not commence at the correct time and subsequently the ovaries and testes will not perform their normal fertility function with the maturation and release of eggs in woman and the production of sperm in men alongside their role in producing the sex hormones. The underlying cause of the failure in production of LH and FSH is the impairment of the hypothalamus to release the hormone GnRH which in normal circumstances induces the production of LH and FSH (Pic.1). Without the correct release of GnRH the pituitary gland is unable to release LH and FSH which in turn prevents the ovaries and testes from functioning correctly (Pic.2). HH can occur as an isolated condition with just the LH and FSH production being affected or it can occur in combined pituitary deficiency conditions such as CHARGE syndrome.

Sixteen different gene defects have so far been described that can cause Kallmann syndrome or other forms of HH through a disruption in the production or activity of GnRH. The genes involved cover all forms of inheritance and no one gene defect has been shown to be common to all cases which makes genetic testing and inheritance prediction very problematic. Males with hypogonadotropic hypogonadism are often born with an unusually small penis (micropenis) and undescended testes (cryptorchidism). At puberty, most affected individuals do not develop secondary sex characteristics, such as the growth of facial hair and deepening of the voice in males. Affected females usually do not begin menstruating at puberty and have little or no breast development. In some people, puberty is incomplete or delayed.

In Kallmann syndrome, the sense of smell is either diminished (hyposmia) or completely absent (anosmia). This feature distinguishes Kallmann syndrome from most other forms of hypogonadotropic hypogonadism, which do not affect the sense of smell. Many people with Kallmann syndrome are not aware that they are unable to detect odors until the impairment is discovered through testing. The features of Kallmann syndrome vary, even among affected people in the same family. Additional signs and symptoms can include a failure of one kidney to develop (unilateral renal agenesis), a cleft lip with or without an opening in the roof of the mouth (a cleft palate), abnormal eye movements, hearing loss, and abnormalities of tooth development. Some affected individuals have a condition called bimanual synkinesis, in which the movements of one hand are mirrored by the other hand. Bimanual synkinesis can make it difficult to do tasks that require the hands to move separately, such as playing a musical instrument.

The diagnosis is often one of exclusion found during the workup of delayed puberty. One of the biggest problems in the diagnosis of Kallmann syndrome and other forms of HH is the ability to distinguish between a normal constitutional delay of puberty and Kallmann syndrome (KS) or hypogonadotropic hypogonadism (HH).

The main biochemical parameters in men are low serum testosterone and low levels of the gonadotropins LH and FSH, and in women low serum oestradiol and low levels of LH and FSH. For both males and females with constitutional delay of puberty, endogenous puberty will eventually commence without treatment. However a delay in treatment in a case of KS/HH will delay the physical development of the patient and can cause severe psychological damage.

The condition has a low prevalence, estimated at 1 in 4,000 for male HH cases overall and 1:10,000 for Kallmann syndrome. It is three to five times more common in males than females. Though whether this is a true gender imbalance or a reflection on how difficult KS / HH is to diagnose correctly in males and females has yet to be fully established.

Associated disease
- cryptorchidism; undescended testicles at birth, occurs in 30% of KS/HH cases
- secondary osteoporosis or osteopenia
- hypogonadism
- hypogonadotropic hypogonadism
- anosmia
- color blindness
- cleft palate
- congenital heart disease

Complications
- failure to start or fully complete puberty in both men and women
- lack of testicular development in men; size < 3 ml
- primary amenorrhoea or failure to start menstruation in women
- poorly defined secondary sexual characteristics in both men and women
- infertility

Risk factors
- family health history

Impact on fertility

Women with KS or HH have an advantage over the men as their ovaries normally contain a normal number of eggs and it sometimes only takes a couple of weeks of treatment to achieve fertility while it can take males up to two years of treatment to achieve fertility. Males with KS are often born with an unusually small penis (micropenis), undescended testes (cryptorchidism) and have azospermia or severe oligozoospermia, spontaneous recovery of gonadal axis function is possible. This would involve the use of ART where sperm can be harvested directly from the testes even if no sperm are present in the ejaculate. Proper management of patients with Kallmann syndrome usually allows them to attain normal reproductive health.

Prevention

Kallmann syndrome cannot be prevented, but you can decrease risk factors severity. To prevent mutations, life style changes may be advised such as avoidance of harmful radiation, exposure to radioactive substances and in the case of pregnant women, protecting against teratogens.

Symptoms

- total lack of sense of smell (anosmia) or markedly reduced sense of smell (hyposmia), which is defining feature of Kallmann syndrome; it is not seen in other cases of HH (approximately 50% of HH cases occur with anosmia and can be termed as Kallmann syndrome)
- cleft palate or other craniofacial defects
- unilateral renal agenesis or aplasia; absence or non-functioning of one of the kidneys
- micropenis, occurs in less than 5 to 10% of KS/HH cases
- undescended testes (cryptorchidism)
- non-obstructive azoospermia
- neural hearing defects
- synkinesis or mirror movements of hands
- dental defects
- normal stature, but there can be an increase in height if treatment is delayed, due to the lack of testosterone or estrogen causing excess bone growth in the arms and legs

Therapies

Self therapy

Self/alternative therapy does not cure KS but you can treat the symptoms with some practical self-help measures.

- **Diet**
  Healthy diet does not guarantee higher fertility. Salt limitation is advised for patients with congestive heart failure.

- **Activity**
  Common activity restrictions are not obligatory. Activity limitations are appropriate in patients with certain forms of congenital heart disease or seizures.

Conventional medicine

Pharmacotherapy

**Hormone replacement therapy (HRT)**

The aim for hormone replacement therapy (HRT) for both men and women is to ensure that the level of circulating hormones (testosterone for men and estrogen/progesterone for women) is at the normal physiological level for the age of the patient. At first the treatment will produce most of the physical and psychological changes seen at puberty, with the major exception that there will be no testicular development in men and no ovulation in women. After the optimum physical development has been reached HRT for men will continue to ensure that the normal androgen function is maintained; such as libido, muscle development, energy levels, hair growth and sexual function. In women, a variety of types of HRT will either give a menstruation cycle or not as preferred by the patient. HRT is very important in both men and women to maintain bone density and to reduce the risk of early onset osteoporosis. The fertility treatments used for both men and women would still include hormone replacement in their action. There are range of
different preparations available for HRT for both men and women, a lot of these, especially those for women are the same used for standard HRT protocols used when hormone levels fall in later life or after the menopause. For the men testosterone replacement is achieved either by using daily capsules, daily gel or patches, fortnightly injections, three monthly injections or six monthly implants. Tablet/capsule forms of HRT rarely give sufficient testosterone levels suitable for men with KS/HH. The three monthly injection of testosterone undecanoate has become very popular over the past ten years. After the first two injections which are six weeks apart; injections are taken every three months and give good testosterone levels throughout the three-month period with no noticeable tail off of levels at the end of the injection cycle. Some patients only require the injection every six months.

Human chorionic gonadotrophin (hCG) is sometimes used to stimulate testosterone production in men and ovulation induction in women. For men it acts in the same way as LH; stimulating the Leydig cells in the testes to produce testosterone. Common trade names for hCG products include; Pregnyl, Folluthel, Profasi or Choragon. Some men with KS or HH take hCG solely for testosterone production.

Human menopausal gonadotrophin (hMG) is used in to stimulate sperm production in men and for multiple egg production and ovulation induction in women. It contains a mixture of both LH and FSH. In men the FSH acts on the sperm producing Sertoli cells in the testes. This can lead to testicular enlargement but can take anything from 6 months to 2 years for an adequate level of sperm production to be achieved. Common trade names for hMG products include; Menopur, Menogon, Reprohorm or Pergonal. Purified forms of FSH are also available and are sometimes used in conjunction with hCG instead of using hMG. Injections can be intramuscular but are normally taken just underneath the skin (subcutaneous) and are normally taken two or three times a week.

For both men and women, an alternative method (but not widely available), is the use of an infusion pump to provide GnRH (or LHRH) in pulsatile doses throughout the day. This stimulates the pituitary gland to release natural LH and FSH in order to activate testes or ovaries.

Surgical therapy

Patients with Kallmann syndrome and congenital heart disease may need corrective surgery. Patients with cleft lip or palate also need surgical correction.

Assisted reproduction

Assisted reproductive technologies, including in vitro fertilization in combination with intracytoplasmic sperm injection (IVF-ICSI), have been used successfully when male patients with Kallmann syndrome or idiopathic hypogonadotropic hypogonadism do not achieve adequate sperm counts on either GnRH or gonadotropin therapy. ICSI together with testicular sperm extraction (TESE) have reduced the need for donor sperm. Anyway, genetic counseling including PGD should be adapted to each family, taking into account the potential mode of inheritance (autosomal dominant, autosomal recessive, or X-linked recessive), as well as the chance, in sporadic cases, of neomutations. If no spermatozoa are produced sperm donation is the only solution for infertile men.

Fertility treatments for people with KS/HH will require specialist advice from doctors experienced in reproductive endocrinology. There is a good success rate for achieving fertility for patients with KS/HH, with some experts quoting up to a 70% success rate, if IVF techniques are used as well. However there are factors that can have a negative effect on fertility and specialist advice will be required to determine if these treatments are likely to be successful. Fertility treatments involve the administration of the gonadotropins LH and FSH in order to stimulate the production and release of eggs and sperm. Women with KS or HH have an advantage over the men as their ovaries normally contain a normal number of eggs and it sometimes only takes a couple of weeks of treatment to achieve fertility while it can take males up to two years of treatment to achieve fertility.

Find more about related issues

Diagnoses

Erectile dysfunction
The inability (that lasts more than 6 months) to develop or maintain an erection of the penis during sexual activity.
Learn more at: www.fertiltypedia.org/therapy/diag/erectile-dysfunction

Undescended testes
In the case of cryptorchidism one or both testes are absent from the scrotum. It is is the most common etiologic factor of azoospermia in the adult.
Learn more at: www.fertiltypedia.org/therapy/diag/undescended-testes

Non-obstructive azoospermia
Complete absence of sperm in the ejaculate due to testicular failure.
Learn more at: www.fertiltypedia.org/therapy/diag/non-obstructive-azoospermia

Hypogonadism
A medical term which describes a diminished functional activity of the gonads – the testes and ovaries.
Learn more at: www.fertiltypedia.org/therapy/diag/hypogonadism

Amenorrhea
The absence of a menstrual period in women of reproductive age.
Learn more at: www.fertiltypedia.org/therapy/diag/amenorrhea

Organs
Hypothalamus
A region of the forebrain that regulates body temperature, some metabolic processes and governs the autonomic nervous system.
Learn more at: www.fertilitypedia.org/edu/organ/hypothalamus

Ovary
The ovum-producing organs of the internal female reproductive system
Learn more at: www.fertilitypedia.org/edu/organ/ovary

Pituitary gland
An endocrine gland, about the size of a pea, whose secretions control the other endocrine glands and influence growth, metabolism, and maturation.
Learn more at: www.fertilitypedia.org/edu/organ/pituitary-gland

Testes
Male gonads which produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.
Learn more at: www.fertilitypedia.org/edu/organ/testes

Reproductive cells

Leydig cell
The cell found in interstitial tissue of testicles responsible for production of androgens - male hormones.
Learn more at: www.fertilitypedia.org/edu/reproductive-cell/leidy-cell

Oocyte
A female germ cell involved in reproduction.
Learn more at: www.fertilitypedia.org/edu/reproductive-cell/oocyte

Sertoli cells
The cell in seminiferous epithelium responsible for nutrition and development of germ (sperm) cells.
Learn more at: www.fertilitypedia.org/edu/reproductive-cell/sertoli-cell

Spermatogonium
An undifferentiated male germ cell with self-renewing capacity representing the first stage of spermatogenesis.
Learn more at: www.fertilitypedia.org/edu/reproductive-cell/spermatogonium

Biological control

Estradiol
A steroid and estrogen sex hormone produced in the ovaries of females.
Learn more at: www.fertilitypedia.org/edu/biological-control/estradiol

Follicle-stimulating hormone
FSH is a hormone secreted by the anterior pituitary gland. It regulates the development, growth, pubertal matur and reproductive functions of the body.
Learn more at: www.fertilitypedia.org/edu/biological-control/follicle-stimulating-hormone

Gonadotropin-releasing hormone
A releasing hormone responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.
Learn more at: www.fertilitypedia.org/edu/biological-control/gonadotropin-releasing-hormone

Luteinizing hormone
A hormone, that stimulates ovulation and the development of the corpus luteum in females, and the production of androgens in males.
Learn more at: www.fertilitypedia.org/edu/biological-control/luteinizing-hormone

Progesterone
Steroid hormone, secreted by the ovaries, whose function is to prepare the uterus for the implantation of a fertilized ovum and to maintain pregnancy.
Learn more at: www.fertilitypedia.org/edu/biological-control/progesterone

Risk factors

Low GnRH secretion
A condition which results in a small subset of cases of hypogonadotropic hypogonadism due to deficiency in or insensitivity to gonadotropin-releasing.
Learn more at: www.fertilitypedia.org/therapy/rf/low-gnrh-secretion

Low level of estrogen
A diminished level of blood estrogen level.
Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-estrogen

Low level of FSH
A condition with low serum follicle-stimulating hormone (FSH) concentration.
Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-fsh
Low level of LH
A serum luteinizing hormone (LH) levels under normal serum concentration for gender and age.
Learn more at: www.fertilitypedia.org/therapy/if/low-level-of-lh

Low level of testosterone
An abnormally low testosterone production which may occur because of testicular or hypothalamic-pituitary dysfunction.
Learn more at: www.fertilitypedia.org/therapy/if/low-level-of-testosterone

Symptoms

Abnormal sperm morphology
A normal sperm morphology of less than 4% of sperms in an ejaculate.
Learn more at: www.fertilitypedia.org/edu/symptoms/abnormal-sperm-morphology

Absence of menstrual periods
The absence of a menstrual period in a woman of reproductive age.
Learn more at: www.fertilitypedia.org/edu/symptoms/absence-of-menstrual-periods-1

Absence of sperm in ejaculate
The medical condition of a man whose semen contains no sperm.
Learn more at: www.fertilitypedia.org/edu/symptoms/absence-of-sperm-in-ejaculate

Bimanual synkinesis
Involuntary movements on one side of the body mirroring voluntary movements on the other.
Learn more at: www.fertilitypedia.org/edu/symptoms/bimanual-synkinesis

Cleft lip and palate
A cleft lip contains an opening in the upper lip. A cleft palate is when the roof of the mouth contains an opening into the nose.
Learn more at: www.fertilitypedia.org/edu/symptoms/cleft-lip-and-palate

Colour blindness
The inability to distinguish certain colours.
Learn more at: www.fertilitypedia.org/edu/symptoms/colour-blindness

Delayed puberty
An organism has passed the usual age of onset of puberty with no physical or hormonal signs.
Learn more at: www.fertilitypedia.org/edu/symptoms/delayed-puberty

Disturbed sense of smell
A qualitative and quantitative alteration or distortion of the perception of smell.
Learn more at: www.fertilitypedia.org/edu/symptoms/disturbed-sense-of-smell

Heart defects
A defect in the structure of the heart and great vessels which is present at birth.
Learn more at: www.fertilitypedia.org/edu/symptoms/heart-defects

Immobile or dead spermatozoa in semen
A condition in which spermatozoa in semen are either immobile or dead.
Learn more at: www.fertilitypedia.org/edu/symptoms/immobile-or-dead-spermatozoa-in-semen

Increase in height
Bones past their pre-determined length and don’t stop growing.
Learn more at: www.fertilitypedia.org/edu/symptoms/increase-in-height

Infertility
The failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.
Learn more at: www.fertilitypedia.org/edu/symptoms/infertility

Lack of breasts development and menstrual periods
Learn more at: www.fertilitypedia.org/edu/symptoms/lack-of-breasts-development-and-menstrual-periods

Low concentration of sperm
A condition refers to semen with a low concentration of sperm.
Learn more at: www.fertilitypedia.org/edu/symptoms/low-concentration-of-sperm

Low facial and body hair growth
Decrease of facial and body hair in males.
Learn more at: www.fertilitypedia.org/edu/symptoms/low-facial-and-body-hair-growth
Low semen volume
A condition in which a man has an unusually low ejaculate (or semen) volume, less than 1.5 ml.
Learn more at: www.fertilitypedia.org/edu/symptoms/low-semen-volume

Osteoporosis
A chronic condition characterized by low bone mass and increased risk of fracture.
Learn more at: www.fertilitypedia.org/edu/symptoms/osteoporosis

Reduced sperm motility
The decreased ability of sperm cell to move progressively.
Learn more at: www.fertilitypedia.org/edu/symptoms/reduced-sperm-motility

Small penis
An adult penis with an erect length of less than 7 cm or 2.76 inches.
Learn more at: www.fertilitypedia.org/edu/symptoms/small-penis

Small testes
Abnormally small testicular volume.
Learn more at: www.fertilitypedia.org/edu/symptoms/small-testes

Undescended testes
The absence of one or both testes from the scrotum.
Learn more at: www.fertilitypedia.org/edu/symptoms/undescended-testes

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Micro TESE
Microsurgical method used to identify areas of sperm production within the testes with the aid of optical magnification.
Learn more at: www.fertilitypedia.org/edu/therapies/micro-tese

Preimplantation genetic diagnosis
Technology that allows couples with a family history of monogenic disorders, x-linked diseases and chromosomal abnormality have a healthy baby.
Learn more at: www.fertilitypedia.org/edu/therapies/preimplantation-genetic-diagnosis

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

TESE
Removal of a small portion of testicular tissue in order to extract a few viable sperm.
Learn more at: www.fertilitypedia.org/edu/therapies/tese
Sources

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* Testicular sperm extraction (https://en.wikipedia.org/wiki/Testicular_sperm_extraction) — sourced from Wikipedia licensed under CC BY-SA 3.0
