Genetic causes of central hypogonadism have been identified.

Idiopathic or isolated HH (IHH) are cases in which secondary causes of HH have been excluded.
Acquired and syndromic causes of HH include the following: CNS or Pituitary tumors, infiltrative diseases (sarcoidosis, Langerhans cell histiocytosis, hemochromatosis, leukemia, lymphoma and Wegener’s granulomatosis), infection, brain/pituitary radiation, pituitary apoplexy, head trauma, drugs (GnRH agonists/antagonists, Glucocorticoids, Narcotics and Chemotherapy), functional deficiency resulting from chronic systemic illness, eating disorders, hypothyroidism, hyperprolactinemia, diabetes mellitus and Cushing’s disease.

Physiology of Idiopathic hypogonadotropic hypogonadism (IHH) / isolated GnRH deficiency

- Low gonadotropin release
  - Failure of initiation of puberty
  - Absent secondary sexual characteristics and an immature reproductive system.

The prevalence of IHH has been estimated to be between 1 in 4,000 and 1 in 10,000 males. It is reported to be between two and five times less frequent in females.¹

30% of IHH is due to genetic causes. GnRH neurons migrate from the nasal placode to their final destination in the hypothalamus. When this is disrupted, the resulting phenotype is Kallmann syndrome (KS), which is clinically characterized by hypogonadotropic hypogonadism and anosmia. Both chromosomal abnormalities and single gene mutations have been identified in patients with IHH and KS.²

There is an entity called Normosmic Idiopathic Hypogonadotropic Hypogonadism (nIHH) which is distinguished from Kallmann syndrome.

Some genes (FGFR1, FGF8, PROKR2, PROK2, CHD7) have been associated with both Kallmann syndrome and nIHH.

Clinical presentation of Kallmann syndrome:

In Pre-puberty –
- Anosmia (suspect when there is already a positive family history)

In Adolescence –
- Suspect if incomplete or absent puberty after age 13.
- Primary amenorrhoea is present in 90% of IHH.
- There is little or no breast development, some may have normal breast development.
- Sparse or normal pubic hair (since adrenals are functional)
- Absent pubertal growth spurt.

In Adulthood - Rarely, individuals have normal sexual maturation.
Retarded bone maturation, osteopenia and osteoporosis are frequent, when the gonadotropin deficiency is discovered in adulthood.\textsuperscript{3}

Partial to mild forms are frequent in a minority of women, which is characterized by isolated chronic anovulation, whereas estradiol secretion is adequate for endometrial development, and can be shown by onset of bleeding after progestin administration, as well as by oligomenorrhea. These mild forms have also been reported to have conceived spontaneously.

**Diagnosis:**
Clinical and laboratory findings are consistent with hypogonadotropic hypogonadism and there is absence of secondary causes of hypothalamic hypogonadism.

Family history is important.

**Detailed physical examination - secondary sexual characteristics**

Assessment of Olfaction to detect hyposmia / anosmia, exclude eating disorders, excessive physical activity, and chronic underlying conditions.

Body mass index, body fat estimation.

**Laboratory tests** - levels of LH, FSH, PRL and estradiol, often low.

In very mild form, in only a minority of women, nIHH can be characterized by isolated chronic anovulation, whereas estradiol secretion is almost normal.

The test with intravenous administration of 100 µg GnRH reflects the severity of the gonadotropin deficiency. Layendecker et al. had divided gonadotropin deficiency into three degrees of severity on the basis of tests, with the administration of Progesterone, Clomiphene citrate and GnRH. Patients having degree 3a or 3b have a chance of recovery of menstruation and fertility, but for patients with degree 3c, the only chance of becoming pregnant is after treatment with gonadotropins.\textsuperscript{4}

Exclude Hyperprolactinemia, Global Anterior Pituitary insufficiency and an associated endocrine disorder that may be a part of syndromic forms of IHH.

Magnetic resonance imaging (MRI) of the brain and olfactory bulbs – important in expansive, infiltrative or malformative disorders.

Renal ultrasound examination – to rule out renal malformation or agenesis.

Pelvic sonography – to know the size of the uterus, endometrial thickness and ovarian development.
Bone mineral density - especially in those with osteoporotic risk factors, such as glucocorticoid treatment and smoking.

**Management:** The choice of therapy is determined by the goal of treatment.

Treatment options include sex steroids, gonadotropins, and pulsatile GnRH administration.

The young women who exhibit a lack of development of the secondary sexual characteristics, should be treated with Estrogens, initially with low doses (1 mg estradiol p.o.). After approximately six months, when breast development has been optimized, replacement doses of estradiol and progestogens should be administered.

In women with nIHH, who wish to become pregnant, pulsatile GnRH stimulation can be used. Intravenous pulsatile administration of GnRH mimics normal cycle dynamics with the resulting ovulation of a single follicle. This therapy offers a clear advantage over treatment with gonadotropins, which involves higher rates of both multiple gestation and ovarian hyper-stimulation syndrome. The rate of conception is approximately 30% per ovulation cycle for both types of treatment.

Recombinant FSH - provides a low risk of hyper-stimulation syndrome.

In cases of severe form of IHH at a concentration of serum LH below 1.2 mIU/ml, it is necessary to add a preparation containing FSH and LH, or recombinant LH, since FSH itself does not lead to luteinisation of granulosa cells. It is also recommended to follow it, with administration of progesterone for luteal phase support. This achieves greater pregnancy rates, but increases the risk of ovarian hyper-stimulation and the development of multiple pregnancies.

**Nutritional Hypothalamic Dysfunction:**

'Starvation' and 'dieting' may lead to menstrual and fertility disorders. There is an increase in height, weight and body fat that usually occurs just before menarche, and at this time, girls begin developing an unhealthy relationship with body weight and food. This is related to socio-cultural influences that focus on body image and weight. Most eating disorders first develop in adolescence itself. In healthy adult women, a short-term calorie restriction diet (800–1,100 kcal/per day) does not change the menstrual rhythm.

When dietary restriction persists for more than one cycle and weight loss occurs, it is followed by suppression of ovulation. Moderate dietary restriction and weight loss in normal cyclic women leads to a reduction of estradiol levels with almost normal LH levels, which is Functional Hypothalamic Amenorrhea (FHA).
Severe starvation in healthy women for two and half weeks induces a reversal of LH pulses to prepubertal patterns. Women with FHA have reduced central GnRH drive, resulting in low FSH and LH levels, which causes anovulation.

The most serious eating disorders, such as Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder are classified as Psychiatric illnesses, and therefore are not in the purview of this discussion.

**Athletic Amenorrhea:** The physiological and psychosocial health benefits of exercise are well established, but we should not forget that, intense exercise can cause adverse health effects. First described in 1997, the 'Female Athletic Triad' is a syndrome that includes disordered eating, amenorrhea and osteoporosis. Athletic amenorrhea has been described in not only professional sportswomen, but also women practicing recreational exercises. Intense recreational exercises can cause ovulatory dysfunction.

FHA is estimated to affect up to 5% of women of reproductive age and is the cause of 35% of women undergoing evaluation for secondary amenorrhea.

A prospective study by Rauh et al showed that high school female athletes with disordered eating and oligomenorrhea/amenorrhea have a reduced BMD (bone mineral density) & hence should be monitored.⁶

**Eating disorders and Athletic Amenorrhea management:**
- Identify the behavior that needs to be modified.
- Promote psychosocial harmony, restoring ovulation and menstrual cyclicity.
- Cognitive behavior therapy with relaxation techniques are advised.
- Adequate caloric intake is ensured.
- 1,500 mg calcium citrate/400 units vitamin D per day.
- Before the plan of ovulation stimulation in order to become pregnant, a healthy weight should be established.⁷

**Summary:**

Hypogonadotropic hypogonadism, either congenital or acquired, is characterized by low GnRH leading to low FSH & LH, which results in amenorrhea and absence or delayed secondary sexual characteristics. This can be treated by estrogen and gonadotropins or GnRH, depending on whether the girl needs treatment for secondary sexual characteristics or infertility.
References: