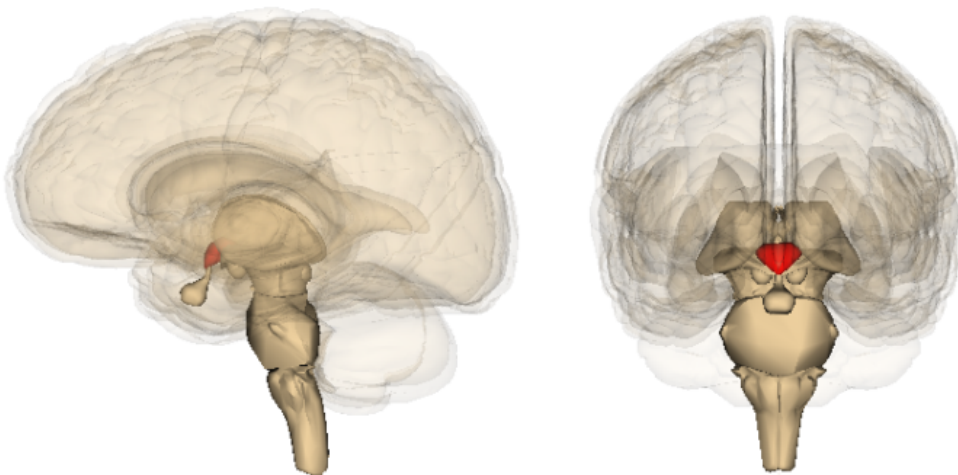


Hypothalamic–Pituitary–Gonadal (HPG) Axis Differentials

[See online here](#)

The endocrine system of the body consists of endocrine glands which produce metabolic changes through the secretion of chemicals called hormones. The Pituitary gland is considered the 'Master' gland of the body. Hormones produced by different endocrine glands have different mechanism of actions. The hypothalamic-pituitary- gonadal axis is a system of interrelated endocrine glands that work like a single entity with a series of communications that regulate hormone secretion between them.



The Hypothalamus

The [Hypothalamus](#) is an area of the brain which controls a lot of functions in the body. It also affects sections of various endocrine glands, specifically the secretion of pituitary glands. Relevant to the hypothalamic-pituitary-gonadal axis, the hypothalamus secretes GnRH that travels via the hypophyseal portal system to the anterior pituitary.

Other hormones secreted from the hypothalamus include thyrotropin-releasing hormone, corticotrophin releasing hormone and growth releasing hormone, all which exert their effects on the pituitary gland.

The Pituitary Gland

Under the influence of GnRH, the **Pituitary gland** itself controls the secretion of

gonadotropic hormones such as LH and FSH that exert the final effects of the axis.

Similarly, other endocrine glands like the **adrenals** and **thyroid glands** are also **activated by hormones from the pituitary gland which include** thyroid stimulating hormones and adrenocorticotrophic hormone.

Like, in other stimulating hormones, inhibitory hormones or factors are also produced. These help in the regulation of these hormones in the body. **Positive and negative feedback mechanisms** regulate the amount of hormones in the blood.

Hypothalamic–Pituitary–Gonadal (HPG) Axis



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The hypothalamic–pituitary–gonadal axis (HPG axis) includes the **hypothalamus**, **pituitary gland**, and **gonadal glands** working together in a loop, through which production of hormones can be regulated. These glands work as if they are a single entity.

The downstream products of the hypothalamic–pituitary–gonadal pathway are regulated through the **negative feedback mechanism**. **Spermatogenesis**, i.e., the production of sperms in the testes, is stimulated by the gonadotropin-releasing hormone (GnRH) from the arcuate nucleus in the hypothalamus.

How does the gonadal axis work?

The hypothalamus secretes **GnRH** in a pulsatile fashion, which travels down to the **anterior pituitary gland** and binds to the receptors on the pituitary gland.

LH (luteinizing hormone) and **FSH** (follicle stimulating hormone) are released from the pituitary gland. Both these hormones enter the **blood stream** flow to the **testes** where LH stimulates the **Leydig cells** to produce **testosterone**, which acts on the **Sertoli cells** stimulating the **production of sperms**.

LH binds the **LH receptors** and promotes the conversion of **cholesterol** to **pregnenolone** through **protein kinase activity**. Pregnenolone is a precursor of testosterone. **Testosterone** is also required for other important biological processes, like the development of primary and secondary sexual characteristics, increasing libido and epiphyseal closure.

FSH stimulates the **Sertoli cells** to produce **androgen binding globulin (ABG)** and **inhibin**. **ABG** binds to **testosterone** from the **Leydig cells** and keeps it available in the **seminiferous tubules** and **other target tissues**.

Inhibin has more of a negative feedback role; it helps in regulating **spermatogenesis** and inhibiting **FSH, LH** and **GnRH** production.

Raised testosterone levels in the blood stimulate the release of inhibin, which causes negative feedback on the pituitary and hypothalamus, decreasing the production hormones in the pituitary gland.

Inhibition of the enzyme, **aromatase**, results in an increase in FSH production suggesting that FSH regulation is more dependent on **estradiol** than testosterone.

In females

GnRH promotes the **release of LH and FSH** which act on the **ovaries** and produce **estrogen** and **inhibin**. A decrease in testosterone and DHEA, with raised estrogen, leads to female **primary sexual characteristics** in the fetal stage. Later in the pubertal age development, female **secondary sexual characteristics** occur.

Estrogen regulates the menstrual cycle and **inhibin** inhibits the hormone, **activin**, which usually stimulates **GnRH production**.

LH surge promotes **ovulation** and **estradiol** promotes the **growth of endometrium**. Increased levels of estrogen and inhibin produces **negative feedback** changes on the pituitary and hypothalamus.

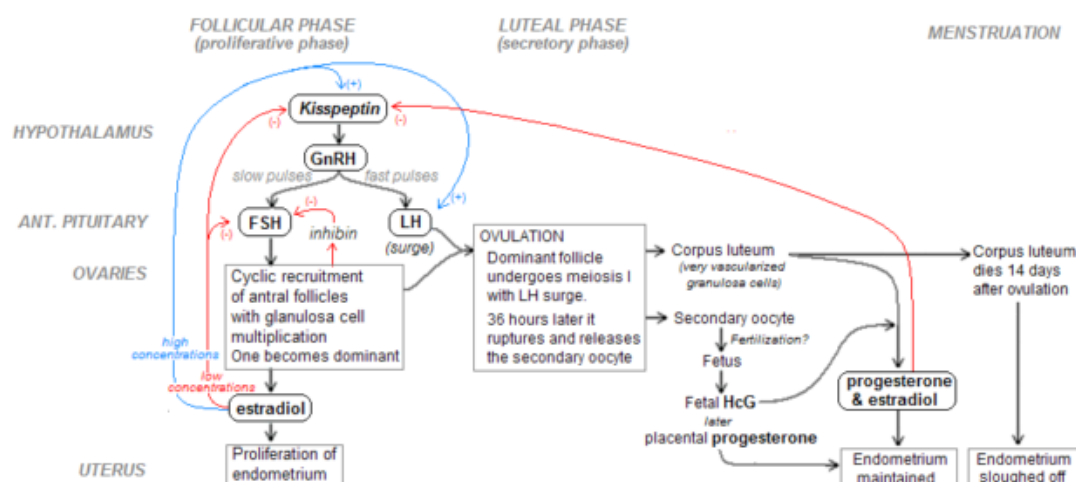


Image: "Menstrual cycle and hormonal changes." by Npatchett. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Role of Androgen-Binding Protein (ABP)

ABP is synthesized by **Sertoli cells** and is later secreted in the **seminiferous tubules**.

This binds to [testosterone](#) and maintains a high concentration of testosterone in the testes. The concentration of the hormone, testosterone, is approximately 50 times more in the testes than in the blood.

Metabolic fate of testosterone

1. Binds to the androgen receptors in the target tissues.
2. Converted to DHEA-dihydrotestosterone at the target tissues by the action of 5-alpha-reductase.
3. Or converted to estradiol by the action of aromatase.

Primary sexual characteristics: Include the growth and development of the testes and penis in males.

Secondary sexual characteristics: Include the development of facial and pubic hair, increased muscle mass and voice changes, as well as the development of the [larynx](#).

Maturation of HPG axis in males

GnRH secretion starts in the intrauterine life in the fetal stage of life. This leads to primary sexual characteristics. Its production decreases in the neonatal period and in the childhood stage, until **puberty** when pulsatile secretion of GnRH occurs and testosterone is produced. Secondary sexual characteristics are produced in the body after puberty until the adult stage of life, the production of GnRH and testosterone increases and, in the later part of adulthood, it starts decreasing.

Hypothalamic-Pituitary-Gonadal (HPG) Axis Differentials

Due to the **disturbance** of hypothalamic-pituitary-gonadal (HPG) axis, the development of sexual characteristics is **delayed** leading to many different **complications** in males and females. It can be due to a **central cause**, i.e pituitary or hypothalamic disturbance or due to **local primary diseases of the gonads**.

Associations of this condition include:

1. Hypospadias
2. Micropenis
3. [Cryptorchidism](#)
4. Mumps
5. Use of various drugs

To find the cause of [hypogonadism](#), the following investigations should be done:

1. FSH level
2. LH level
3. Prolactin level
4. Estradiol levels
5. Seminal fluid examination
6. Thyroid function test
7. Karyotyping

Still, if a clear diagnosis cannot be made, **testicular tissue testing** (testicular biopsy) and **LH releasing hormone stimulation tests** should be done.

Hypogonadism

Female hypogonadism

Causes of hypogonadism in females are almost the same as those of males, except that instead of **Klinefelter's syndrome**, **Turner syndrome** occurs. Features of Turner syndrome include short stature, webbed neck, high arch palate, short fourth metacarpals, and wide-spaced nipples.

Male hypogonadism

Primary hypogonadism or hypergonadotrophic variety

The type of hypogonadism in which pituitary and hypothalamus are working normally but the problem lies within the gonads, is called primary hypogonadism. **Causes of primary hypogonadism include:**

1. Genital trauma
2. Autoimmune destruction
3. Mumps orchitis

Side effects of drugs:

1. Cyclosporine
2. Chemotherapeutic agents

Congenital disorders:

1. Klinefelter's syndrome
2. Bilateral anorchia

Secondary hypogonadism or hypogonadotropic variety

The type of hypogonadism in which pituitary or hypothalamic secretions are decreased leading to the decreased growth of gonads and other characteristics is called secondary hypogonadism.

Causes include:

1. Idiopathic causes
2. Post infectious state of CNS
3. Prolactinoma
4. Damage to the hypothalamus or pituitary via radiations, tumor, infiltrative trauma
5. [Hereditary hemochromatosis](#)
6. Congenital disorders like [Kallman's syndrome](#)

Side effects of drugs:

- a. Opiates
- b. Glucocorticoids
- c. Leuprolide (used in prostate cancer)

Signs and symptoms of hypogonadism

Hypogonadism can begin during:

- Fetal development,

- Before puberty, or
- During adulthood. Signs and symptoms of the disease depend on when the condition develops

During fetal development:

Impaired growth of external sex organs occurs in fetal life leading to any of the following:

- Female genitals
- Ambiguous genitals — genitals that are neither clearly male nor clearly female
- Under-developed male genitals

At Puberty:

It leads to delayed puberty, incomplete or lack of normal development. It can cause:

- Decreased development of muscle mass
- Lack of deepening of the voice
- Impaired growth of body hair
- Impaired growth of the [penis and testicles](#)
- Excessive growth of the arms and legs in relation to the trunk of the body
- Development of breast tissue ([gynecomastia](#))

In adulthood:

Hypogonadism may alter physical masculine characteristics and impair normal reproductive function.

Signs and symptoms may include:

- [Erectile dysfunction](#)
- [Infertility](#)
- Decrease in beard and body hair growth
- Decrease in muscle mass
- Development of breast tissue (gynecomastia)
- Loss of bone mass ([osteoporosis](#))

As testosterone decreases, men have symptoms similar to those that females have after **menopause**: fatigue, decreased sex drive, difficulty concentrating and hot flashes.

References

[How the Gonadal Axis Works](#) via [geekymedics.com](#)

[Hypogonadism](#) via [medlineplus.gov](#)

[Male hypogonadism](#) via [mayoclinic.org](#)

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