Reproductive

FSH

Analyte Information

Follicle-stimulating hormone

Introduction

Follicle-stimulating hormone (FSH, also known as follitropin) is a glycoprotein hormone secreted by the anterior pituitary gland. Its molecular mass is 33 kDa. The intact FSH molecule is a noncovalently-linked dimer containing alpha and beta subunits. The FSH alpha subunit is homologous to the alpha subunits of several other glycoprotein hormones, including luteinizing hormone (LH), thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG).

The generic term "gonadotropins" is used for luteinizing hormone (LH) and FSH because those two hormones control the functional activity of the gonads.

Each hormone has a unique beta subunit[1]. FSH has a beta subunit of 118 amino acids (Follitropin subunit beta, Fig.1), which is responsible for its specific biological action as well as its interaction with the FSH-receptor. The sugar component of the hormone is composed of fucose, galactose, mannose, galactosamine, glucosamine, and sialic acid, the last being critical to FSH's biological half-life.

Fig1.: Follitropin subunit beta
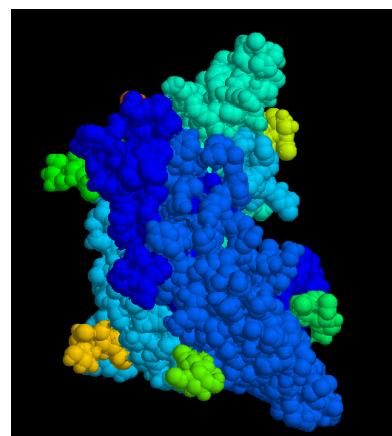
Biosynthesis

FSH release at the anterior pituitary gland is controlled by pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus. GnRH release is pulsatile, resulting in episodic release of both FSH and LH[2]. Their production and secretion is regulated by a complex balance of endocrine feedback systems from the gonads involving a number of steroids (estradiol, testosterone and progesterone) and peptides (inhibins, activins, follistatin) hormones[3,4]. Positive and negative feedback centers of the hypothalamus are involved in these regulation processes (Fig.2).

Fig.2: The regulatory feedback loop of the hypothalamic-pituitary-gonadal axis[5]
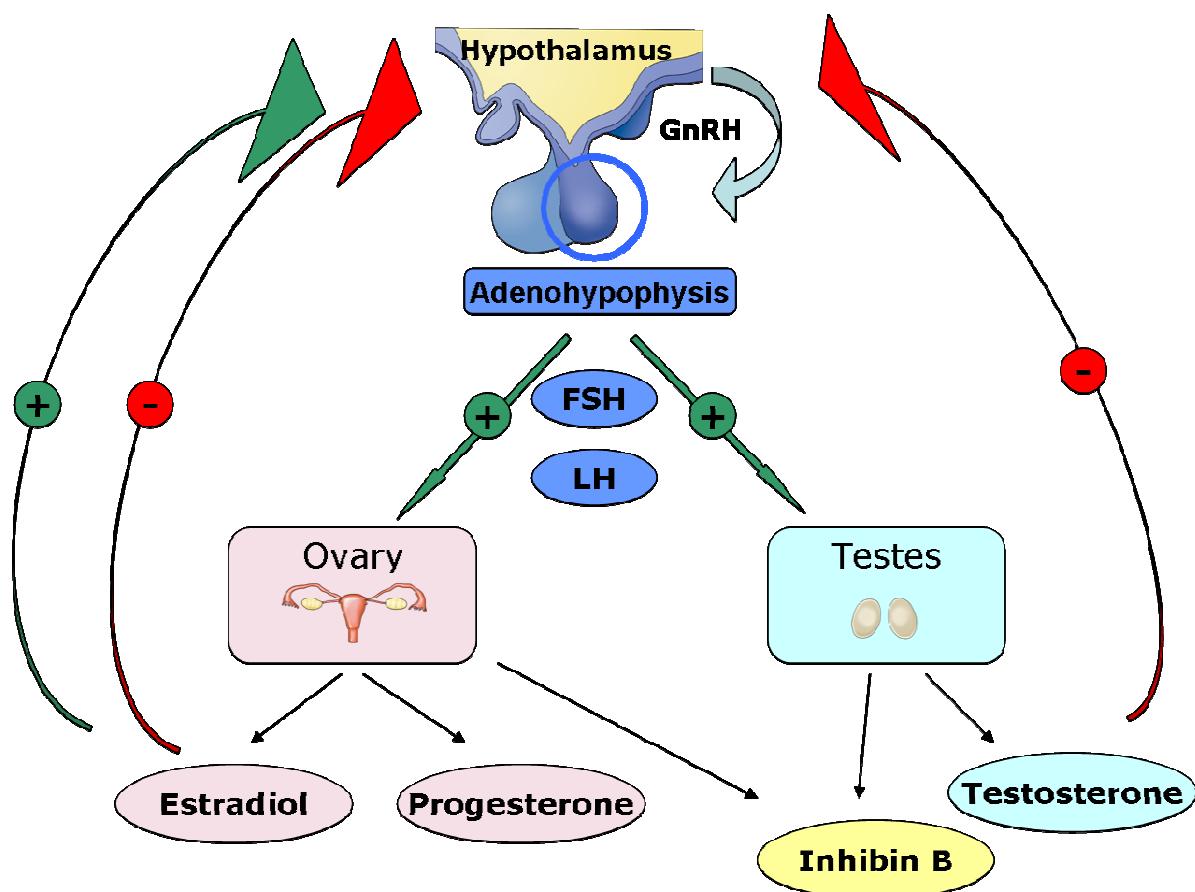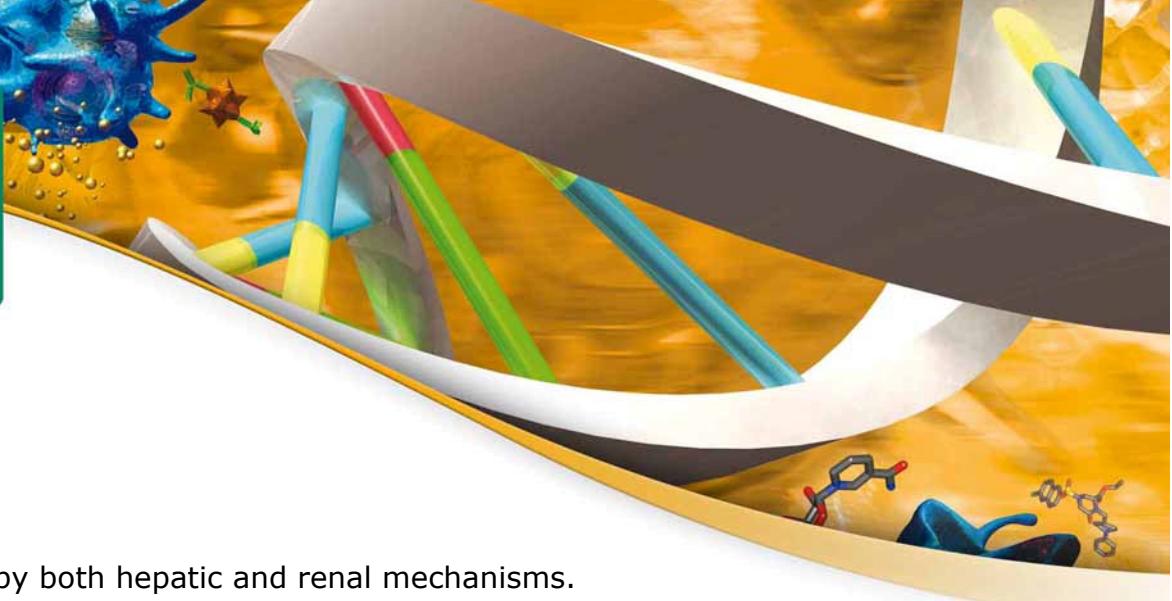
Metabolism

FSH is cleared by both hepatic and renal mechanisms.

The biological half-life of FSH is 3 - 4 hours, longer than that of LH (20 minutes) and shorter than hCG (24 hours).

Physiological Function

In both males and females, FSH stimulates the maturation of germ cells. FSH binds to specific cell membrane receptors on ovarian granulosa cells and testicular Sertoli cells.

In females, FSH stimulates the growth of ovarian follicles and together with LH promotes secretion of estrogens by the maturing follicle. A few days before the onset of menstrual flow, serum levels of progesterone and estrogens (primarily estradiol) decrease and no longer suppress the release of FSH; consequently, FSH levels increase slightly around day three of menstrual flow. This increase of FSH initiates the growth and maturation of a cohort of ovarian follicles. As estradiol is released from growing follicles, FSH concentration falls and remains low throughout the follicular phase. By days five to seven, a single follicle (dominant or Graafian) is selected for further growth. The sharp increase in estradiol production by the dominant follicle (possibly along with a decrease in gonadotrophin surge-attenuating factor) causes a positive effect on the hypothalamus and pituitary glands and rapid GnRH pulses occur. FSH and LH receptors respond with an increase either in number or in affinity for corresponding gonadotropin. There is a rise in FSH at midcycle triggered by estradiol. During the luteal phase, FSH is suppressed by negative feedback from estradiol until a lesser FSH peak, occurring near the end of the cycle, sets off the follicular maturation of the next cycle (Fig.3).

In men, FSH stimulates testicular synthesis of inhibin B and androgen binding protein in Sertoli cells (the "nurse" cells of the testes, part of the seminiferous tubules). FSH acts with LH and testosterone to stimulate the maturation of seminiferous tubules and spermatogenesis. Inhibin B is the protein that down-regulates FSH synthesis and thereby inhibites FSH secretion[6]. FSH enhances the production of androgen-binding protein by the Sertoli cells of the testes by binding to FSH receptors on their basolateral membranes[7], and is critical for the initiation of spermatogenesis.

Fig.3: Menstrual cycle

OVULATION

FOLLICULAR PHASE   LUTEAL PHASE

Anterior pituitary hormones — LH, FSH

Ovarian hormones — Estradiol, Progesterone

Relative thickness of uterine lining

2 4 6 8 10 12 14 16 18 20 22 24 26 28
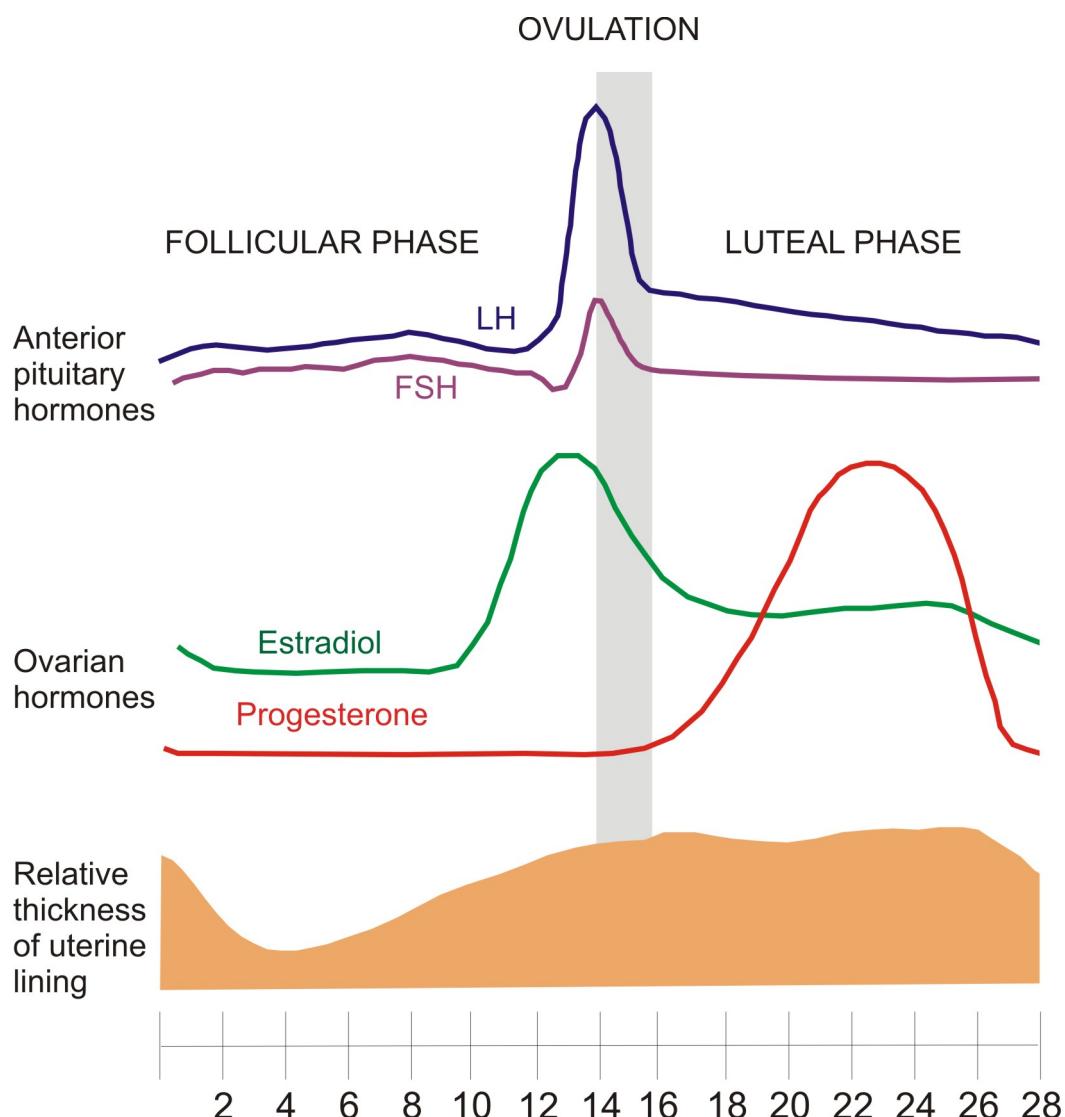
Summary of physiological function

In females, FSH stimulates the growth of ovarian follicles and together with LH promotes secretion of estrogens by the maturing follicles.

In males, FSH stimulates spermatogenesis by germ cells in the testes.

Levels

The pulsatile release of FSH can make
a single blood level measurement of FSH difficult to interpret
clinically. It is recommended to follow concentrations over a sufficient
period of time to obtain proper information about FSH blood level.

As FSH levels do not exhibit diurnal cyclicality, fasting is not necessary prior to
the collection of blood samples.

Normal FSH levels vary with gender, age and menstrual cycle phase. It is
recommended to measure FSH levels on the 3rd day of the menstrual cycle.

FSH levels are low during childhood. In children who undergo precocious puberty
of pituitary or central origin, FSH levels may be in the higher range associated
with reproductive age.

During the reproductive years, typical levels are between 1-20 IU/L.
Physiologically high FSH levels are seen during the FSH surge.

FSH levels increase significantly in women after menopause. High levels of FSH
indicate that normal restricting feedback from the gonad is absent, leading to
unrestricted pituitary FSH production.

Typical FSH levels[8] of children and adult males and females are given in table 1.
For each assay, the relevant reference values are shown in the appropriate
Instructions for Use (IFU).

Table 1: Typical FSH levels

Specimen (serum or plasma)	Reference interval (mIU/mL)*
Infants 2-11 months	
male:	0.19 – 11.3
female:	0.1 – 11.3
Adult	
male:	1.4 – 15.4
female	
follicular:	1 - 10
ovulatory peak:	6 - 17
luteal:	1 - 9
postmenopausal:	19 - 100

* Numerical values based on WHO 2nd IRP 78/549 reference materials

Diagnostic utility – prospects and possibilities

Measurement of serum FSH levels provides a useful marker of many disorders of the reproductive system.

Increased FSH levels are usually associated with subfertility and/or infertility.

Altered FSH levels can be found in broad spectrum of disorders, e.g.:

Elevated FSH levels

- premature menopause (premature ovarian failure)
- poor ovarian reserve (premature ovarian ageing)
- Turner syndrome (gonadal dysgenesis)
- Swyer syndrome
- congenital adrenal hyperplasia (certain forms)
- testicular failure

Decreased FSH levels

- hypogonadism
- amenorrhea
- polycystic ovary syndrome (PCOS)
- hirsutism
- Kallmann's syndrome
- hypothalamic suppression
- hypopituitarism
- hyperprolactinemia
- gonadotropin deficiency and gonadal suppression therapy
- mental anorexia
- precosiuos puberty

Diagnostic utility – Practical applications

FSH measurement is often used in conjunction
with other tests (LH, AMH, inhibin B, testosterone, estradiol and
progesterone) in cases of infertility or pituitary, hypophyseal or gonadal disorders
in both men and women.

FSH measurement may be used to determine if a woman has problems
conceiving, if she has irregular menstruation or to evaluate menopausal status.
In children, FSH and LH may be used when puberty does not appear at an
appropriate age (either too late or too soon). It may be an indication of more
serious problems involving the hypothalamus, pituitary gland, gonads (ovaries or
testes) or other systems.

In women

Diagnosis of menstrual cycle disorders and amenorrhea

Precocious puberty
Laboratory tests used to support this diagnosis are: LH and FSH levels,
and GnRH stimulation test. 17-hydroxyprogesterone is used to exclude
nonclassical adult-onset adrenal hyperplasia in cases of expected GnRH-
independent precocious puberty.

Delayed puberty (primary amenorrhea)
Serum measurement of gonadotropins (LH, FSH) is recommended. Low
concentrations may indicate pituitary failure while elevated levels indicate
gonadal failure.

Secondary amenorrhea
There are many possible causes of amenorrhea, including pregnancy,
hypothyroidism and hyperprolactinemia among others. PRL, hCG, TSH, FT4
and anti-TPO levels may be measured in addition to LH and FSH,. In cases
of unclear cause, estrogen status should be determined.

Polycystic ovary syndrome (PCOS)
Elevated LH levels together with normal or low FSH levels (ratio LH to FSH
is higher then 2.5) suggest a possibility of polycystic ovary syndrome.
PCOS is associated with androgen hyperproduction and decreased
synthesis of ovarian estrogens. This is compensated for by increased
synthesis of these hormones in the periphery, so that serum estrogen
levels remain normal. On the other hand, androstenedione, testosterone
(both total and free) and AMH concentrations are usually elevated.
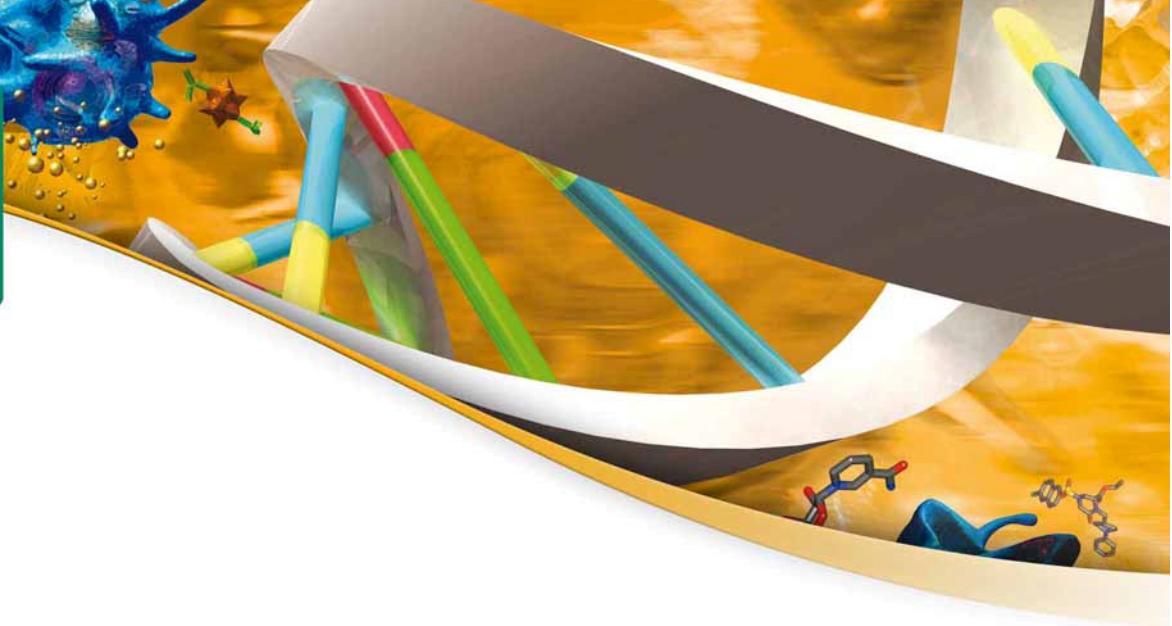
Mild hyperprolactinemia is frequently present. 17-hydroxyprogesterone is also commonly measured to test for 21-hydroxylase deficiency.

Differential diagnosis of sterility

Measurements of LH, FSH, PRL, TSH, AMH and Inhibin B are usually taken.

Hypophyseal insufficiency

LH and FSH levels are expected to be low in this case. GnRH stimulation tests are used to confirm the diagnosis.

Ovarian insufficiency

LH, FSH, estradiol and AMH are usually measured. High gonadotropin concentrations and low estradiol level support this diagnosis.

In men

Kallmann's syndrome (hypogonadotrophic hypogonadism)

LH, FSH and testosterone levels are lower than normal.

Hypergonadotrophic hypogonadism

LH and FSH levels are elevated and testosterone levels are decreased.

Male infertility

Gonadotropin (LH and FSH), Inhibin B and testosterone levels are measured in this case.

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