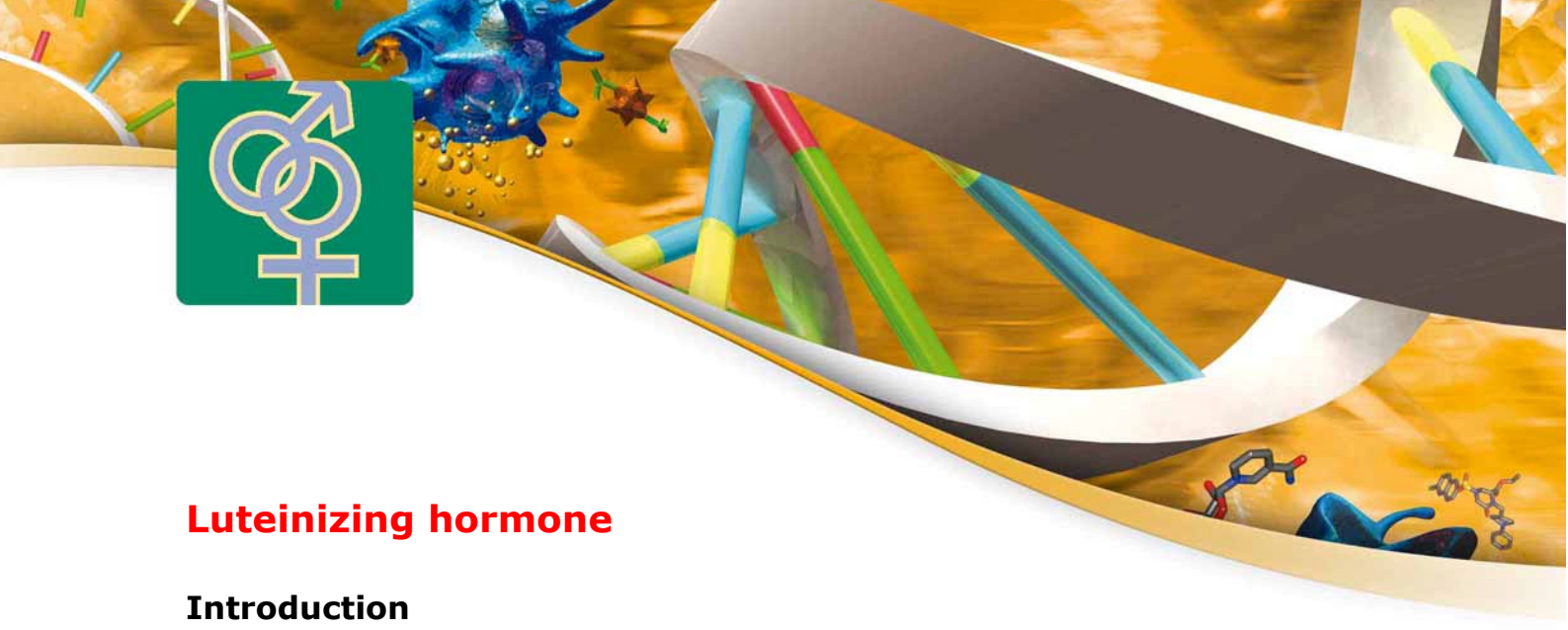
Reproductive

LH

Analyte Information



Luteinizing hormone

Introduction

Luteinizing hormone (LH, also known as lutropin or interstitial cell-stimulating hormone) is a glycoprotein of molecular mass 29.4 kDa. The hormone is released by the anterior pituitary gland (adenohypophysis) in response to gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LH-RH).

The generic term "gonadotropins" is used for LH and follicle-stimulating hormone (FSH) because those two hormones control the functioning of the gonads.

The LH molecule is a heterodimeric (noncovalently-linked) glycoprotein. Each monomeric unit is a glycoprotein molecule; one alpha and one beta subunit form the full functional protein. The alpha subunits of LH, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (hCG) are identical. The beta subunits are specific to the respective hormone[1]. LH has a beta subunit of 121 amino acids (LHβ) that determines its specific biological action and is responsible for its specific interaction with the LH receptor.

The LH beta subunit contains an amino acid sequence that exhibits large homology with that of the beta subunit of hCG, and both stimulate the same receptor. However, the hCG beta subunit contains an additional 24 amino acids. The hormones differ in the composition of their respective sugar moieties.

Biosynthesis

The production and secretion of both LH and FSH is stimulated by gonadotropin-releasing hormone from the hypothalamus. GnRH release is pulsatile, resulting in episodic release of both LH and FSH from the pituitary gland[2].

The production and secretion of these hormones is regulated by a complex interaction of endocrine feedback systems. There are two separate feedback centers in the hypothalamus: a tonic negative feedback center in the basal medial hypothalamus, and a cyclical positive feedback center in the anterior regions of the hypothalamus[3].

Low concentrations of estradiol during the follicular phase affect the negative feedback center, whereas high concentrations of estradiol before the midcycle LH peak trigger the positive feedback center. LH production is again suppressed during the luteal phase by the negative feedback from progesterone combined with estradiol[3] (Fig. 1).

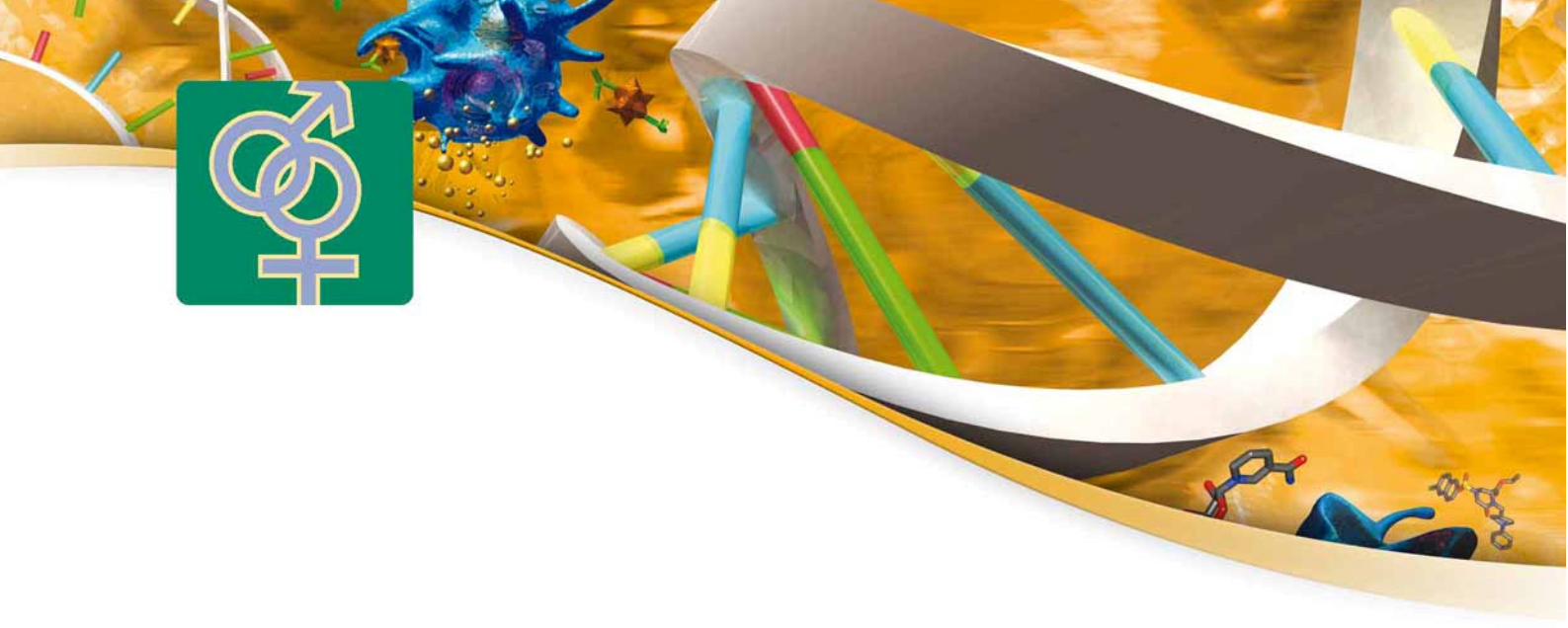
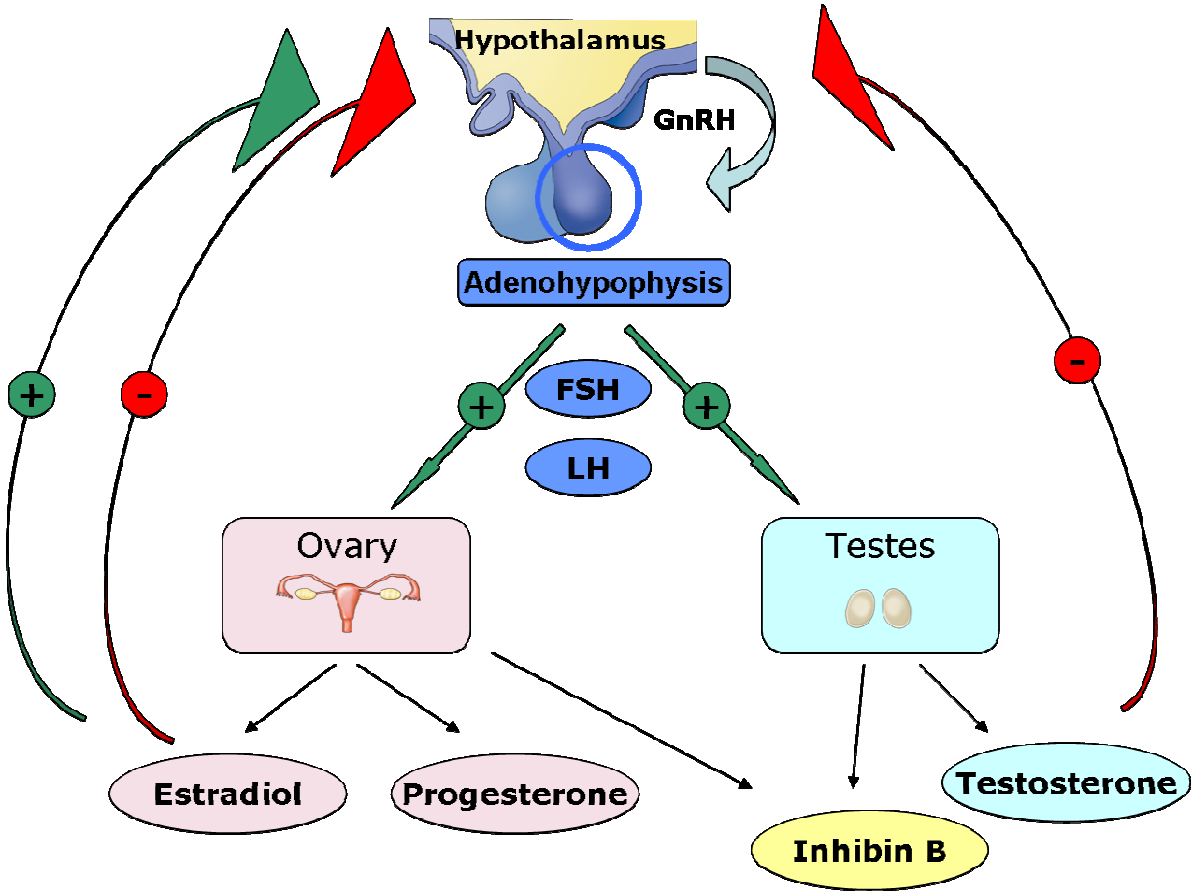


Fig.1: The regulatory feedback loop of the hypothalamic-pituitary-gonadal axis[3]



Metabolism

LH is cleared by both hepatic and renal mechanisms. The biological half-life of LH is 20 minutes, shorter than that of FSH (3–4 hours) or hCG (24 hours).

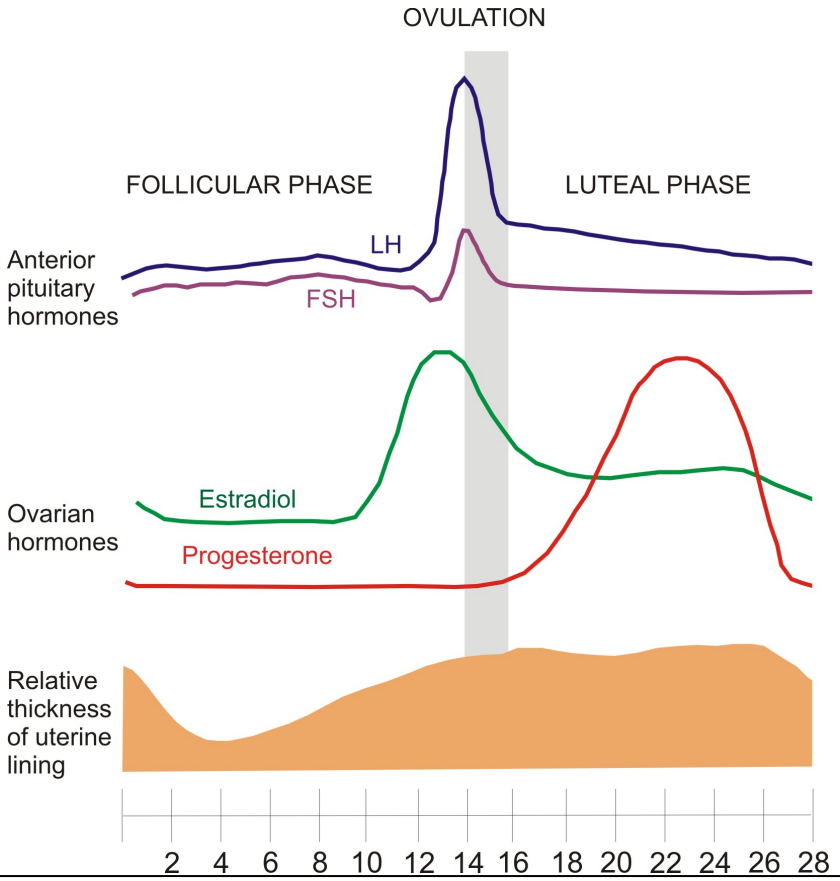
Physiological Function

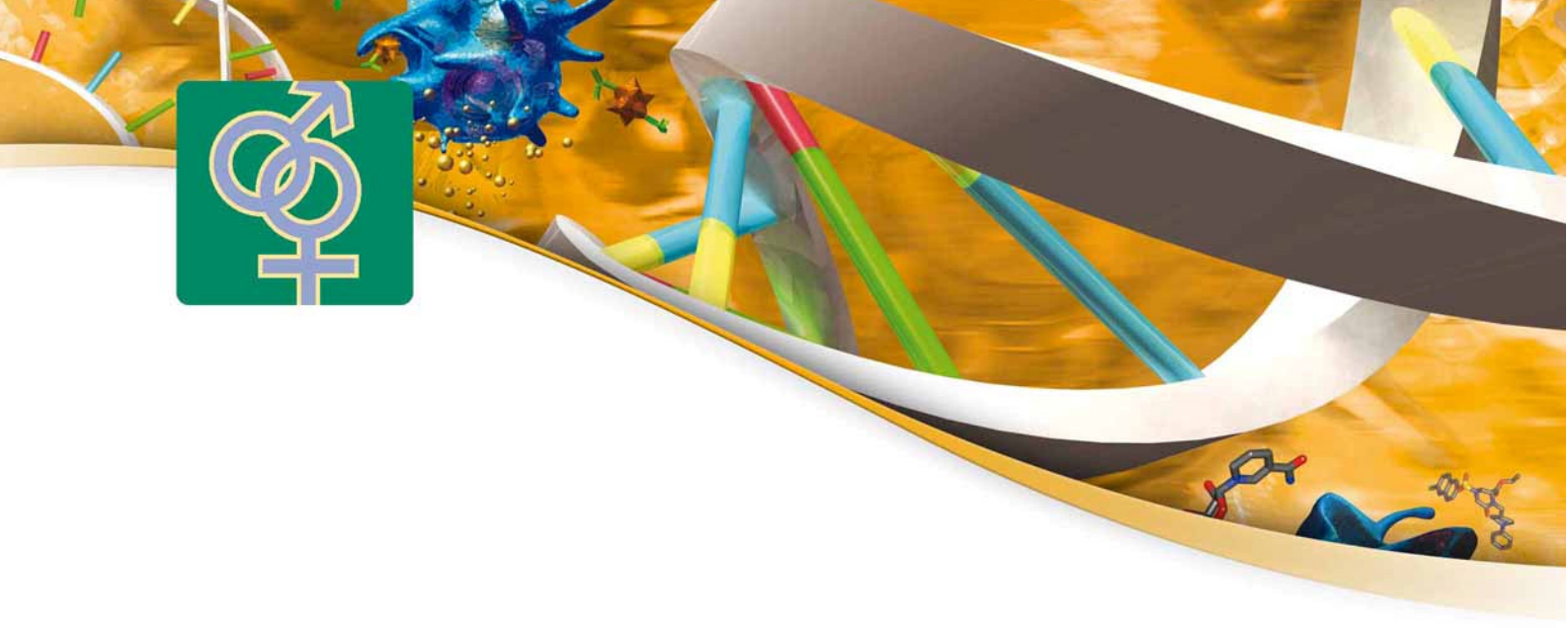
LH is essential for reproduction in both males and females.

In pre-pubescent children, the peripheral levels of gonadotropins and gonadal steroids are very low. During puberty, pituitary sensitivity to GnRH increases, resulting in elevated gonadotropin secretion, gonadal steroid secretion stimulation, and development of secondary sex-specific characteristics.

In females, LH is one of important hormones that controls the menstrual cycle, which is necessary for reproduction. It is commonly divided into three phases: the follicular phase, ovulation, and the luteal phase. Follicular growth is initiated by FSH, specifically affecting granulosa cells. As a result, estradiol levels gradually increase during the follicular phase. With this rise in estradiol levels, LH receptors are also expressed on the maturing follicle. In the late follicular phase the increased amount of estradiol exerts positive feedback on the hypothalamus and pituitary glands,[4,5] resulting in a surge (sharp rise) in GnRH levels and a peak in the release of LH and FSH (Fig.2).

Fig.2: Menstrual cycle





One day prior to the LH surge, a peak in estradiol levels is observable. The LH surge is followed by a rupture of the Graafian follicle (mature) and by ovulation[4-6.] This "LH surge" triggers ovulation, which means the egg is released, and the conversion of the residual follicle into a corpus luteum is initiated. The corpus luteum produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first two weeks. In case of pregnancy, luteal function will be further maintained by the action of hCG (a hormone very similar to LH). During the luteal phase, estradiol and progesterone exert negative feedback on the hypophysis, resulting in low LH secretion (Fig.1).

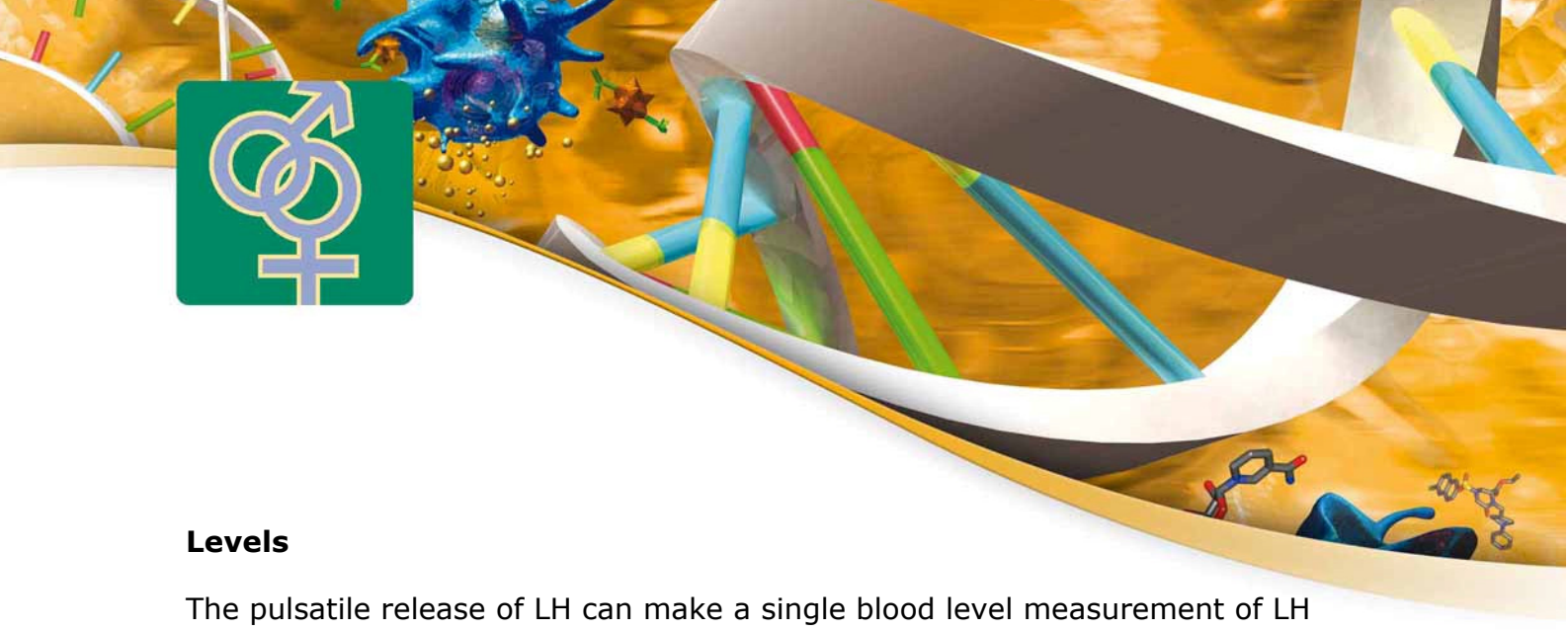
In males, LH binds to specific cell membrane receptors on testicular Leydig cells. LH acts in conjunction with FSH upon the Leydig cells, and is responsible for the production of testosterone to stimulate spermatogenesis.

Summary of physiological function

In pre-pubescent children, LH stimulates gonadal steroid secretion and consequently the development of secondary sex-specific characteristics.

In mature females, LH is responsible for ovulation, stimulation of corpus luteum formation and stimulation of ovarian progesterone synthesis.

In males, LH encourages the development of sperm cells and regulates the production of testosterone by the testes.



Levels

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

As LH levels do not exhibit diurnal cyclicality, the blood samples need not be collected during a state of fasting.

Normal LH levels vary with gender, age and menstrual cycle phase. It is recommended that LH levels be measured on the 3rd day of the menstrual cycle.

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

During reproductive years, typical levels are between 1-20 IU/L. Physiologically high LH levels are seen during the LH surge lasting around 48 hours.

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

Typical LH levels[7] 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).

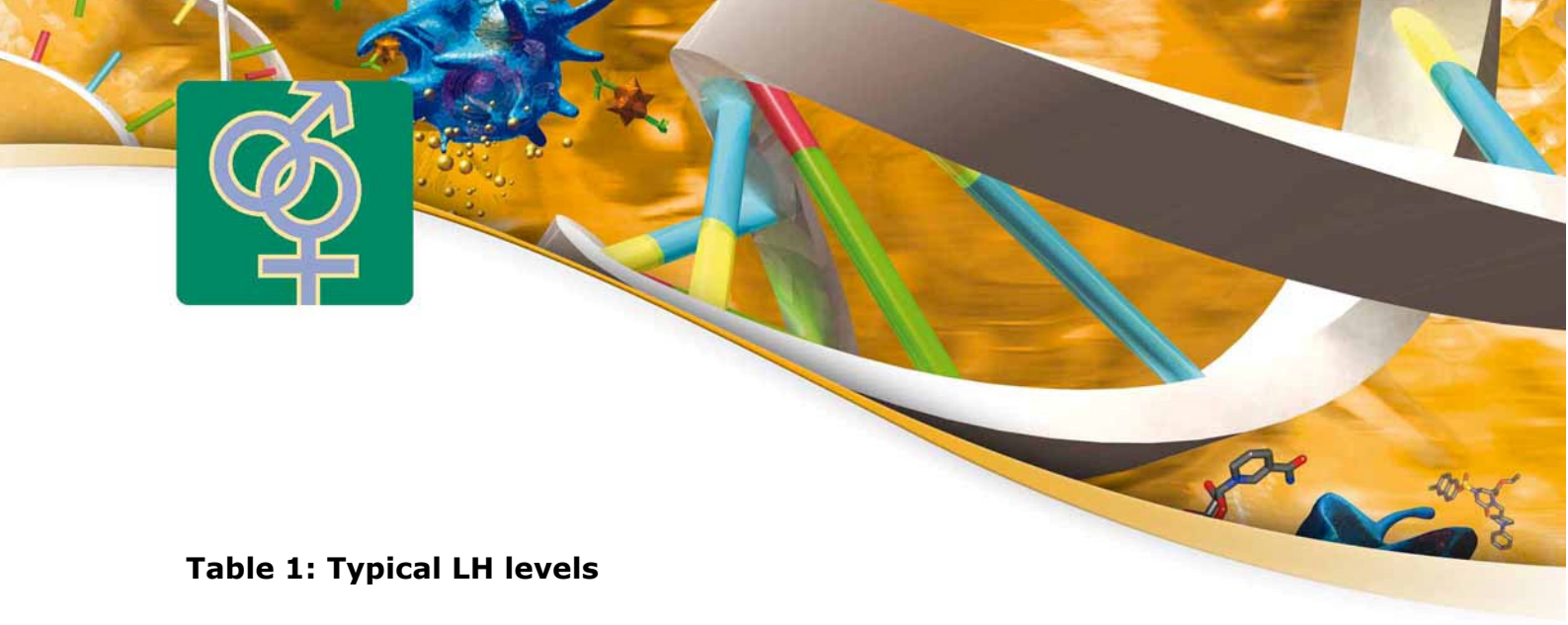
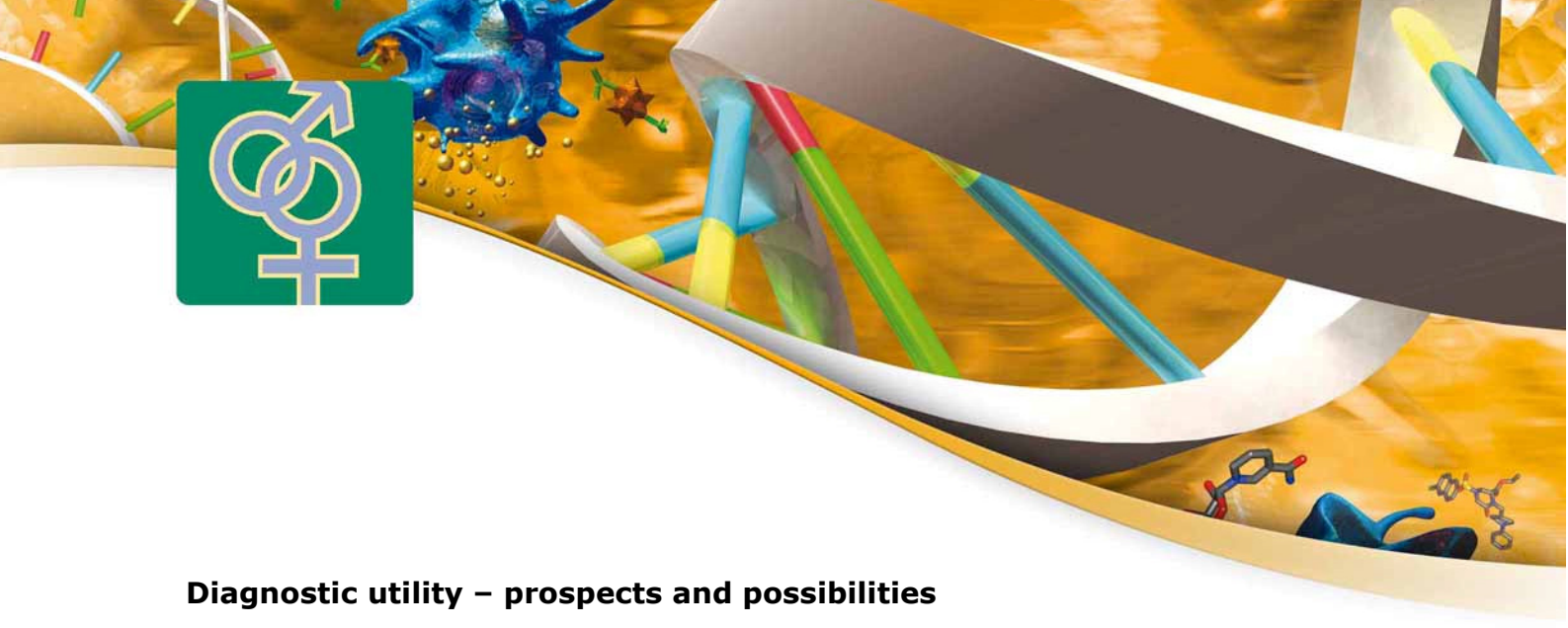


Table 1: Typical LH levels

Specimen (serum or plasma)	**Reference interval** (mIU/mL)*
Cord blood:	0.04 – 2.6
Prepubertal child	
2-11 months:	0.02 – 8.0
1-10 years:	0.08 – 3.9
Puberty	
Tanner stage	
I, Male:	0.04 – 3.6
Female:	0.03 – 3.0
II, Male:	0.26 – 4.8
Female:	0.10 – 4.1
III, Male:	0.56 – 6.3
Female:	0.20 – 9.1
IV-V, Male:	0.56 – 7.8
Female:	0.50 – 15.0
Adult	
Male:	1.24 – 7.8
Female	
Follicular phase:	1.68 – 15.0
Ovulatory peak:	21.9 – 56.6
Luteal phase:	0.61 – 16.3
Postmenopausal:	14.2 – 52.5

* WHO 1st IRP 68/40



Diagnostic utility – prospects and possibilities

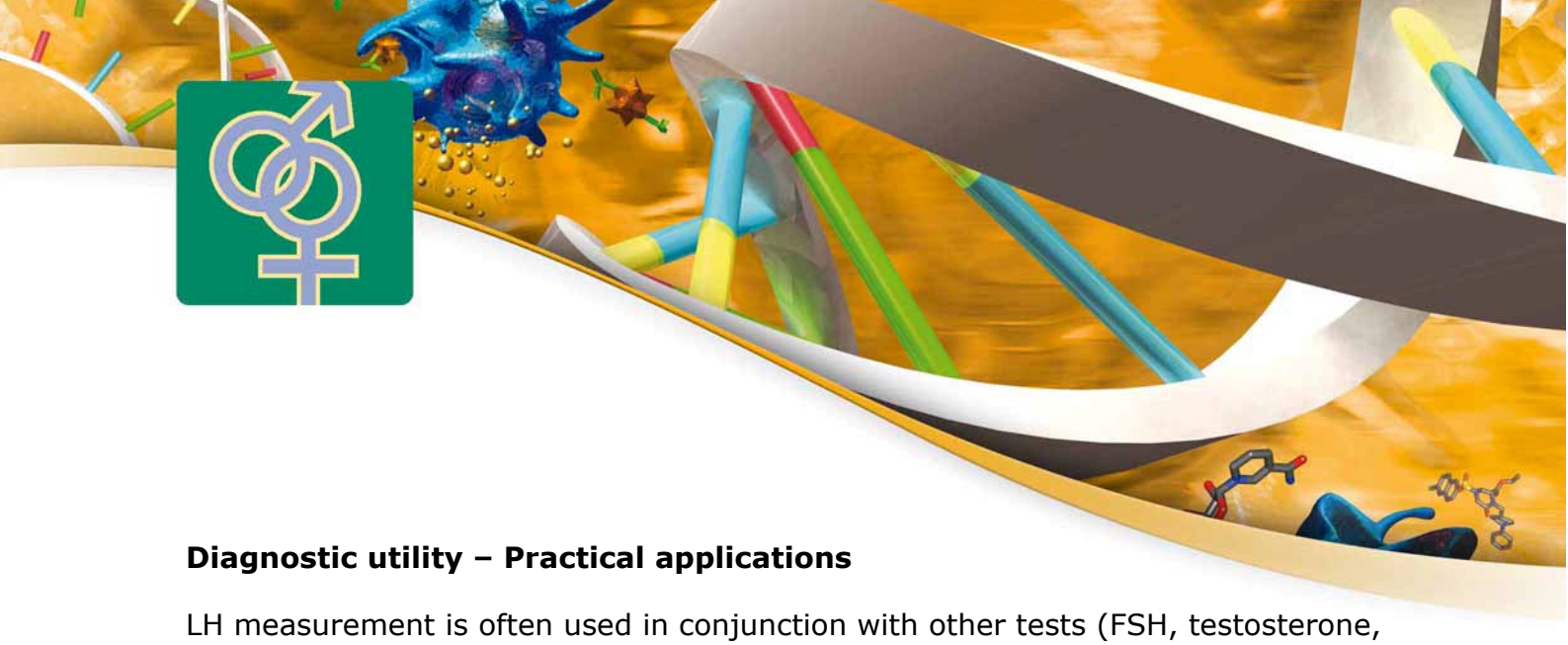
Measurement of serum LH provides a useful marker of many reproductive disorders. Altered LH levels can be found in a broad spectrum of disorders, e.g.:

Elevated LH levels

- premature menopause (premature ovarian failure)
- Turner syndrome (gonadal dysgenesis)
- Swyer syndrome
- polycystic ovary syndrome (PCOS)
- congenital adrenal hyperplasia (certain forms)
- testicular failure
- castration

Decreased LH levels

- hypogonadism
- amenorrhea
- Kallmann's syndrome
- hypothalamic suppression
- hypopituitarism
- hyperprolactinemia
- gonadotropin deficiency and gonadal suppression therapy
- disorder of the hypothalamo-hypophyseal axis
- mental anorexia
- hormonal replacement therapy (HRT)
- precocious puberty



Diagnostic utility – Practical applications

LH measurement is often used in conjunction with other tests (FSH, testosterone, estradiol and progesterone) to determine the cause of infertility in both men and women. LH levels are also useful in the investigation of menstrual irregularities and to aid in the diagnosis of pituitary disorders or diseases involving the ovaries or testes. Furthermore, LH concentration is often considered in cases of suspected early or delayed sexual development in children.

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)

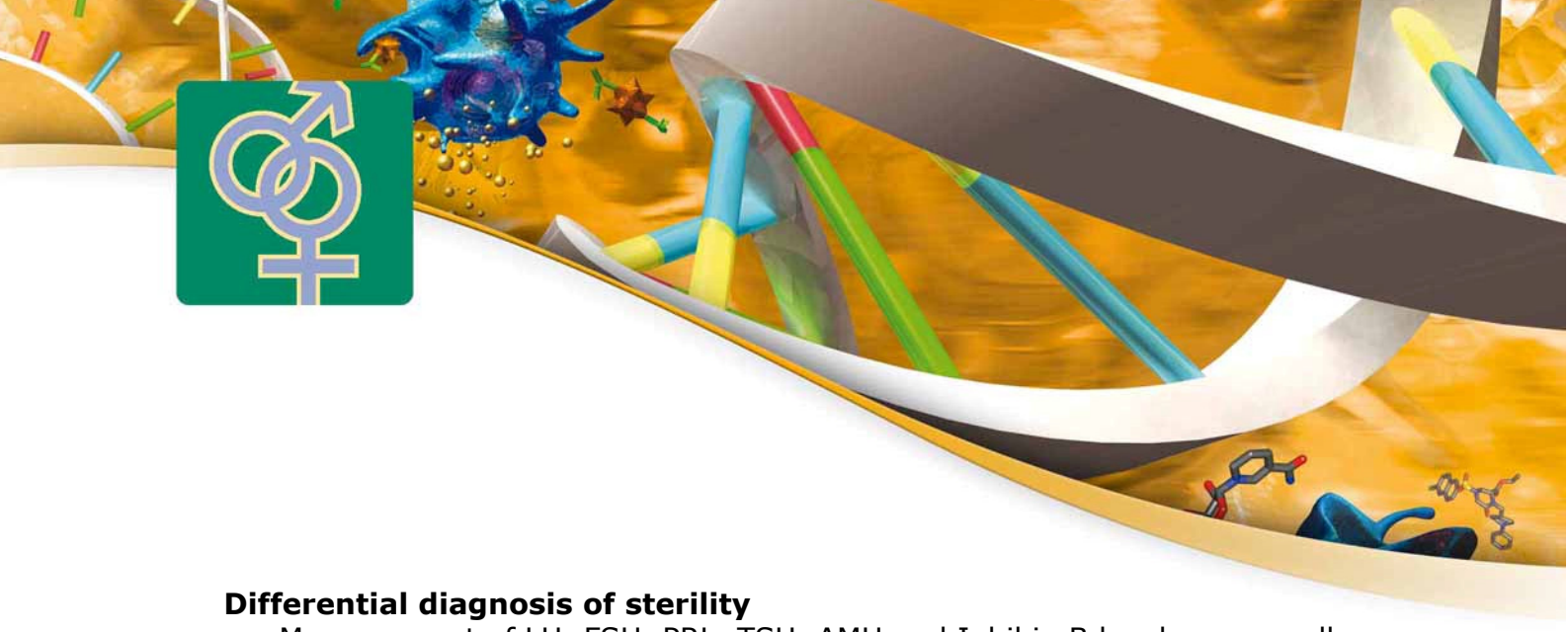
Serum measurement of gonadotropins (LH, FSH) is recommended. Low concentrations may indicate pituitary failure while elevated levels indicate gonadal failure.

Secondary amenorrhea

There are many possible reasons for amenorrhea, including pregnancy, hypothyroidism, hyperprolactinemia and others. In addition to LH and FSH, measurements may be taken of PRL, hCG, TSH, FT4 and anti-TPO levels. In case of unclear cause, estrogen status should also be determined.

Polycystic ovary syndrome (PCOS)

Elevated LH levels together with normal or low FSH levels (ratio of LH to FSH levels greater than 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, concentrations of androstenedione, testosterone (both total and free) and AMH are usually elevated. Light hyperprolactinemia is frequently present. Other measureable parameters include 17-hydroxyprogesterone, which is used to evaluate 21-hydroxylase deficiency.



Differential diagnosis of sterility

Measurement of LH, FSH, PRL, TSH, AMH and Inhibin B levels are usually used.

Hypophyseal insufficiency

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

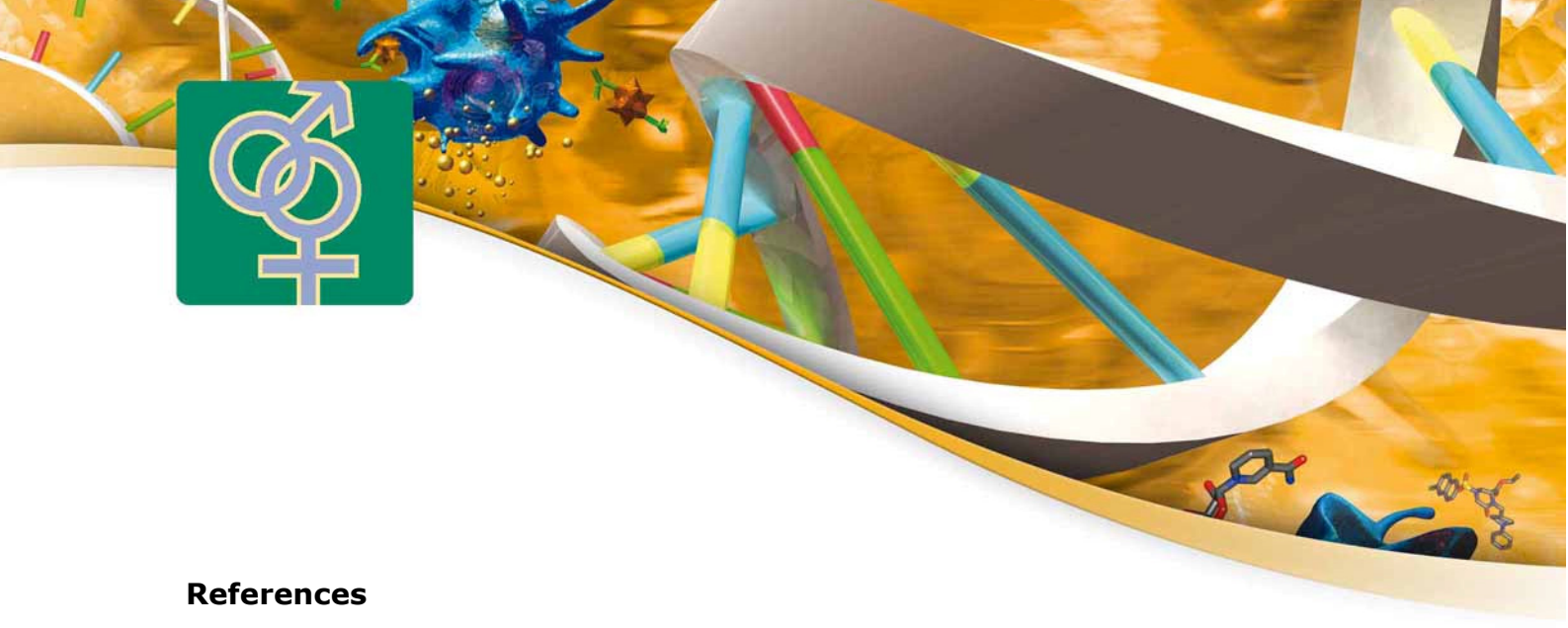
LH, FSH and testosterone levels are lower than normal.

Hypergonadotrophic hypogonadism

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

Male infertility

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



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