

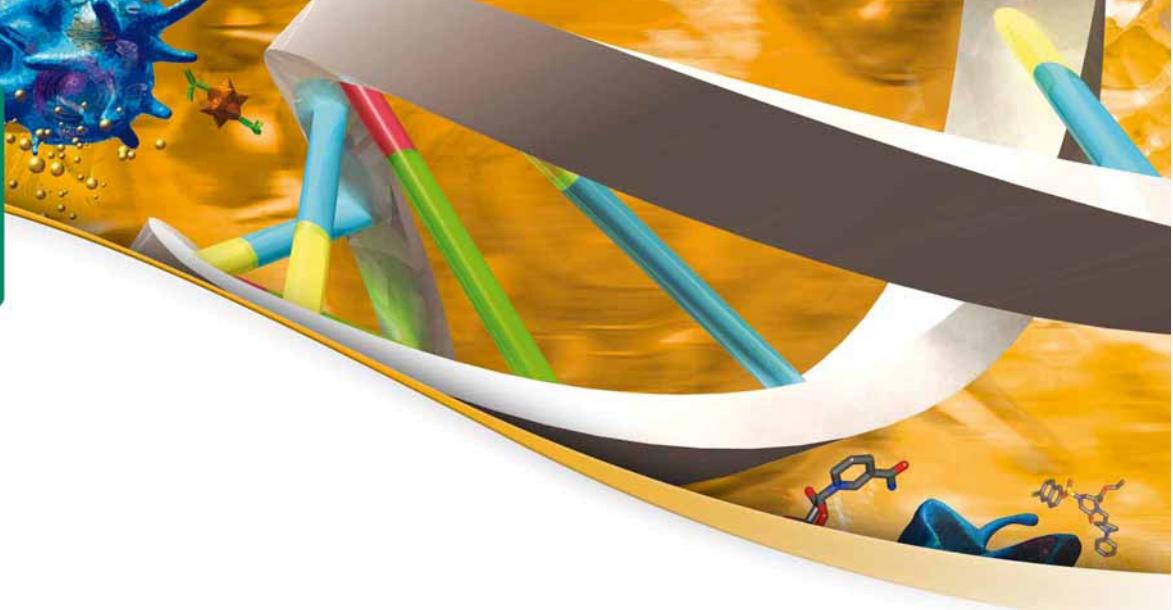


## Reproductive

PRL

Analyte Information





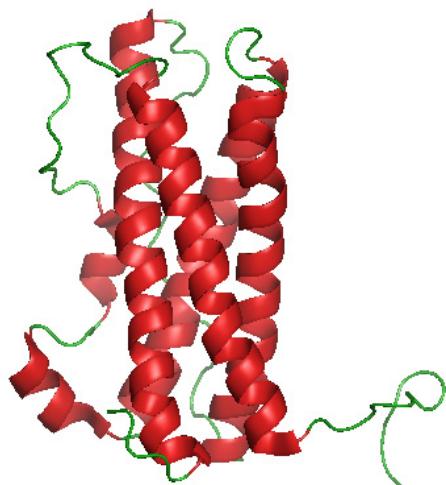
## Prolactin

### Introduction

Prolactin (PRL) is a single-chain polypeptide consisting of 199 amino acids, with a molecular weight of about 23 kDa (Fig.1). The molecule has an extensive sequence homology with growth hormone (GH) and placental lactogen<sup>1</sup>. The prolactin molecule is folded due to the activity of three intramolecular disulfide bridges. Studies have revealed molecular heterogeneity of prolactin in both pituitary extracts and blood<sup>2,3</sup>. It is present in circulation in monomeric (small PRL), dimeric (big PRL) or polymeric (big-big PRL) forms. The monomeric form has the highest bioactivity of the three. Quantitative relations of PRL forms vary under various pathological conditions.

Other names for prolactin include: luteotropin, lactogen, lactotropin, mammatropin, galactopoietic hormone, lactation hormone, lactogenic hormone, and luteotropic hormone (LTH).

**Fig.1: Prolactin**





## Biosynthesis

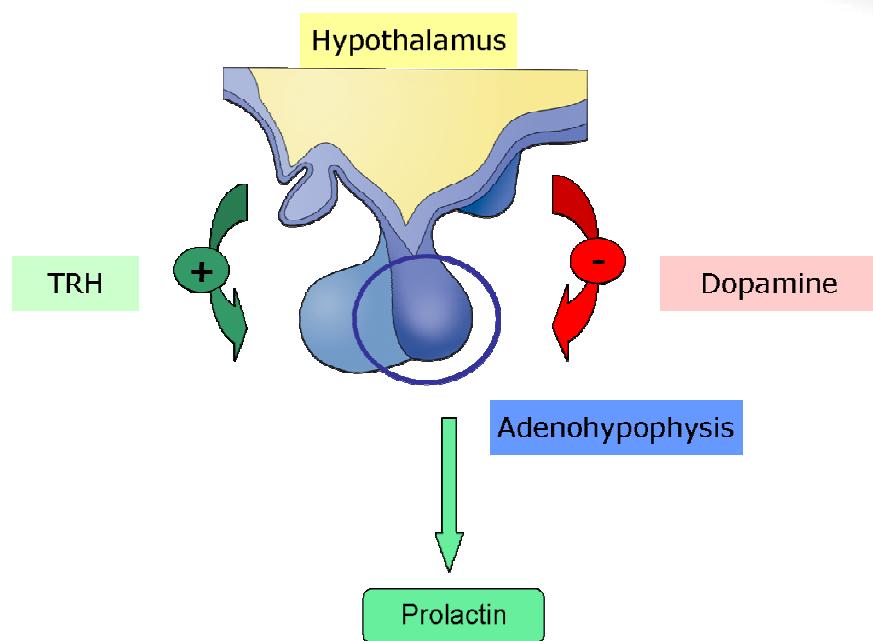
Secretion of prolactin, as of other hormones released by the anterior lobe of the pituitary gland, falls under hypothalamic control. This secretion is regulated by complex mechanisms involving neurotransmitters and endocrine hormones. Many of the regulatory pathways involve hypothalamic secretion of dopamine, which inhibits prolactin secretion<sup>4</sup>.

Prolactin is synthesized and secreted by sex binding lactotrope cells in the adenohypophysis (the anterior pituitary gland). The relative number of these cells is increased in fetal pituitary glands and during pregnancy. Prolactin is also produced in other tissues including the breast, the placenta, the decidua, parts of the central nervous system, the brain and the immune system<sup>5</sup>.

Pituitary prolactin secretion is regulated by neuroendocrine neurons in the hypothalamus, the most important of these being the neurosecretory tuberoinfundibulum (TIDA) neurons of the arcuate nucleus. They secrete dopamine to act on the dopamine-2 receptors (D2-R) of lactotrophs, causing inhibition of prolactin secretion. Thyrotropin-releasing hormone (TRH) has a stimulatory effect on prolactin release. Other endogenous stimulators of prolactin secretion include  $\gamma$ -amino-butyric acid (GABA) serotonin and melatonin. Prolactin secretion is also affected by estrogen levels. High estrogen levels stimulate prolactin secretion by means of inhibition of dopamine synthesis, whereas low estrogen levels are more likely to inhibit prolactin secretion by increasing sensitivity of the hypophysis to dopamine (Fig.2).



**Fig.2: Regulatory control of prolactin release**



## Metabolism

The excretion of prolactin is not fully understood. It may occur partially through urine. The biological half-life of prolactin is 15 – 20 minutes.

## Physiological Function

Prolactin, in conjunction with various estrogens, plays an important physiological role in the initiation and maintenance of mammary gland growth and lactation<sup>1,4</sup>. It is the principal hormone that controls lactation.

In addition, prolactin may have effects on cell growth in other tissues, on immune function (its receptor is present both on stem cells and on T- and B-lymphocytes) and on orgasm.

Prolactin also stimulates proliferation of oligodendrocyte precursor cells. These cells differentiate into oligodendrocytes, the cells responsible for the formation of myelin coatings on axons in the central nervous system<sup>6</sup>.



Particularly when present in high concentrations, prolactin may have inhibitory effects on gonadal function. Prolactin inhibits the secretion of gonadotropin-releasing hormone (GnRH) and its activity in the pituitary gland, and so counteracts gonadotropine activity in the ovaries.

Prolactin also decreases levels of sex hormones — estrogen in women and testosterone in men. It is this inhibition of sex steroids that is responsible for suppression of the menstrual cycle in lactating women as well as lactation-associated osteoporosis.

In men, prolactin strengthens testosterone bonding in the prostate and increases the production of androgen receptors. It has a regulatory on sperm lifetime.

During pregnancy, high circulating concentrations of estrogens promote prolactin production. The resulting high levels of prolactin secretion cause further maturation of the mammary glands, preparing them for lactation by effecting lobular-alveolar differentiation.

Prolactin also has a number of other effects, including contributing to surfactant synthesis in fetal lungs at the end of pregnancy, and to immune tolerance of the fetus by the maternal organism during pregnancy.

After childbirth, prolactin levels fall as the internal stimulus for them is removed.

Suckling by the baby on the nipple then promotes further prolactin release, maintaining the ability to lactate. These signals are carried by nerve fibers through the spinal cord to the hypothalamus, where changes in the electrical activity of neurons that regulate the pituitary gland cause an increase of prolactin secretion.

Prolactin controls milk production (lactogenesis) but not the milk-ejection reflex, which is enabled by the hormone oxytocin (the production of which is also stimulated by suckling). The rise in prolactin fills the breast with milk in preparation for the next feed.



## Summary of physiological function

Maintenance of mammary gland growth and lactation

Maintenance of immune system function

Influence on nervous system

Inhibitory effect on gonadal function

## Levels

Prolactin is present in several bodily fluids, including blood, amniotic fluid, milk, mucosal secretions and cerebrospinal fluid.

Prolactin levels progressively increase during pregnancy, obviously as a result of increased estrogen synthesis in the foeto-placental unit. As with other adenohypophyseal hormones, prolactin is released episodically and varies predictably during the day, with the lowest levels at midday and peaks during REM sleep, and in the early morning.

Levels can also rise after exercise, meals, sexual intercourse, minor surgical procedures<sup>7</sup>, or following epileptic seizures<sup>8,9</sup>.

As prolactin secretion is inhibited by dopamine, persons receiving antipsychotic drugs, which block dopamine, have increased prolactin levels. A wide range of pharmaceuticals increase prolactin levels: phenothiazides, tricyclic antidepressants, methyldopa, haloperidol, chlorpromazine, reserpine, cimetidine and others.

Prolactin increase has also been reported after drinking beer.

Due to the prolactin molecule's significant heterogeneity, bioassays and immunoassays may yield varying results. This may be caused by the presence of different polymeric forms of PRL, as well as by glycosylation, phosphorylation, sulfatation, or degradation. The non-glycosylated form of prolactin is the dominant form secreted by the pituitary gland.

As prolactin exhibits a remarkable diurnal cycle with its maximum during nocturnal sleep, samples for the prolactin measurement should be taken in the morning, at least 3 hours after waking up.

High prolactin levels have been found in amniotic fluid and in foetal membranes. It seems possible that prolactin plays a role in the maturing of foetal lung tissue. Newborns have relatively high prolactin levels after



birth, which decrease during successive months to the low levels common to infants.

Typical prolactin serum levels<sup>10</sup> 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: Prolactin serum levels**

<b>Specimen</b> (serum)	<b>Reference interval</b> (ng/mL)
Cord blood:	45 - 539
Newborn, 1-7 days:	30 - 495
Children,	
Tanner stage	
I, male:	< 10
female:	3.6 - 12
II-III, male:	< 6.1
female:	2.6 - 18
IV-V, male:	2.8 - 11.0
female:	3.2 - 20
Adult,	
male:	3.0 – 14.7
female:	3.8 – 23.2
pregnancy,	
3 <sup>rd</sup> trimester:	95 - 473



## Diagnostic utility – prospects and possibilities

Measurement of serum PRL provides a useful marker for many reproductive and pituitary disorders.

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

### Elevated PRL levels

- hyperprolactinemia
- pituitary adenoma
- hypogonadism
- after epileptic seizure
- prolactinoma (benign tumor of the pituitary gland)
- primary hypothyroidism
- chronic renal failure
- galactorrhea
- amenorrhea
- oligospermia
- emotional stress
- polycystic ovary syndrome (PCOS), in 30 % of patients
- drugs: dopamine blocking or depleting agents, noncatecholamine-dependent agents, H2-receptor blocking agents, tricyclic antidepressants

### Decreased PRL levels

- bulimia
- excess of dopamine
- hypopituitarism



## Diagnostic utility – Practical applications

### Hyperprolactinemia

Hyperprolactinemia (abnormally high levels of prolactin in the blood) is the most common hypothalamic-pituitary disorder encountered in clinical endocrinology<sup>11</sup>. Hyperprolactinemia impairs the gonadal function in both sexes. In women, high blood levels of prolactin often cause hypoestrogenism with anovulatory infertility and oligomenorrhea, amenorrhea, galactorrhea. In men, the most common symptoms of hyperprolactinemia are decreased libido, erectile dysfunction, and infertility.

Hyperprolactinemia may be caused either by dysfunction of regulatory mechanisms (e.g. compression of the pituitary stalk or reduced dopamine levels), or by excess production by a prolactinoma (a pituitary gland adenoma tumour).

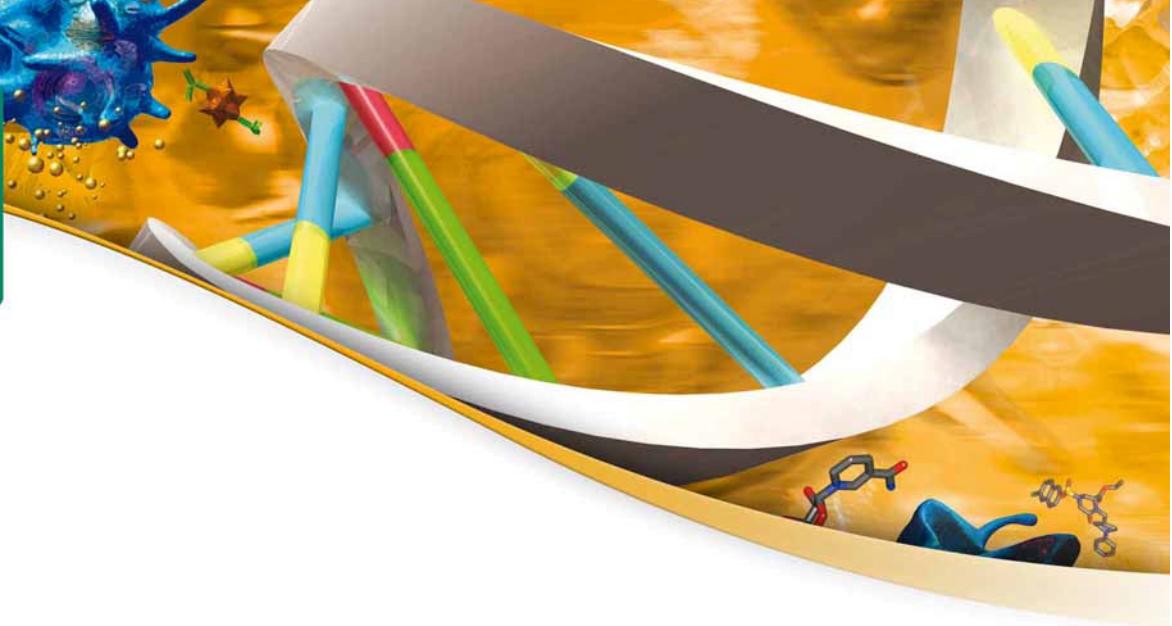
Laboratory diagnostics used in cases of hyperprolactinemia consist mainly of prolactin, TSH and FT4 blood serum measurements to rule out primary hypothyroidism, and pregnancy tests (unless the patient is postmenopausal or has had a hysterectomy). Other biomarkers such as gonadotropins, estrogens, androgens and IGF-1 may be measured as well.

### Differential diagnostics between epileptic seizures and psychogenic non-epileptic seizures

Serum prolactin levels usually rise following an epileptic seizure<sup>10,11</sup>.

### The prolactin secreting pituitary adenomas

Prolactin-secreting pituitary adenomas (prolactinomas) secrete excessive amounts of prolactin and are the most common type of pituitary tumors seen clinically. They are a common cause of gynecological problems including oligomenorrhea, infertility, amenorrhea and galactorrhea. Diagnosis requires a combination of endocrine testing and radiological evaluation<sup>12</sup>.



These pituitary tumors vary significantly in size, from microadenomas to macroadenomas. Macroadenomas may be associated with mass effects such as severe headache, nerve palsies or visual changes. Microadenomas are more subtle<sup>12</sup>.

Prolactinomas are present in men and in women with the same frequency<sup>12</sup>.

### **Indications for prolactin determination:**

#### **In women**

- Menstrual cycle disorders and amenorrhea
- Differential diagnostics of infertility
- Lactation disorders
- Galactorrhea
- Pituitary hyperfunction syndrome diagnostics
- Pituitary insufficiency
- Substitution check-up after pituitary tumour surgery

#### **In men**

- Testicular insufficiency
- Azoospermia, oligospermia
- Galactorrhea
- Pituitary hyperfunction syndrome diagnostics
- Pituitary insufficiency
- Substitution check-up after pituitary tumor surgery



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