



Analyte Monographs alongside the National Laboratory Medicine Catalogue Template

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1 Name and description of analyte

1.1 Name of analyte

Prolactin

1.2 Alternative names

Luteotrophic hormone, luteotropin

1.3 NLMC code: To follow.

1.4. Function(s) of analyte

Prolactin is primarily released by the lactotrophs of the anterior pituitary gland. Its main function is to stimulate the mammary glands within the breast tissue to promote and maintain lactation. Smaller quantities of prolactin are also synthesised in other tissues, including the brain, immune cells, breasts, prostate and the decidua of the uterus in pregnancy. Prolactin also plays a role in a number of other physiological processes including reproduction, metabolism, osmoregulation and immune regulation.

The regulation of prolactin release is controlled by the action of dopamine, also known as prolactin release-inhibiting hormone (PRIH), which is produced in the hypothalamus and acts to suppress prolactin secretion. Other regulatory factors include oestrogen and thyrotropin-releasing hormone (TRH), which promote prolactin release, oxytocin and anti-diuretic hormone (ADH). The primary physiological stimulus for prolactin release is pregnancy and breast-feeding.

2 Sample requirements and precautions

2.1 Medium in which measured

Prolactin may be measured in either serum or plasma.

2.2 Precautions re sampling, handling etc.

Prolactin is measured in its basal state with no suppression/stimulation required. It is a relatively stable analyte that requires no special handling. Excessive venepuncture stress should be avoided.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

Measurement of prolactin is most commonly used in the diagnosis of hyperprolactinaemia and monitoring of subsequent treatment, for example in patients with unexplained galactorrhoea or infertility. It is also measured in patients taking antipsychotic drugs which are known to raise prolactin levels.

3.2 Limitations

Prolactin may be increased in normal physiological states such as pregnancy, lactation and stress.

4 Analytical considerations

4.1 Analytical methods

Prolactin is commonly measured by non-competitive, heterogeneous 'sandwich' immunoassay methods using antibodies which recognise distinct epitopes on the prolactin molecule.

4.2 Reference method

There is no current reference method for prolactin measurement.

4.3 Reference materials

There have been four international standards for prolactin. The first, established in 1978, was WHO IRP 75/504. This was followed by the second international standard, IRP 83/562, the third, IRP 84/500 and most recently the fourth, IRP 83/573 which contains 67mIU of prolactin. However, many commercial assays remain calibrated to IRP 84/500.

4.4 Interfering substances

The presence of macroprolactin is a major analytical concern in prolactin measurement. This is most frequently a biologically inactive complex of prolactin with immunoglobulin G (IgG), 150-170 kDa in size. However, the composition and structure of the macromolecular complex may vary, with autoantibody-bound forms or glycosylated prolactin aggregates also occurring. Macroprolactin is a relatively frequent cause of analytical hyperprolactinaemia (estimated to be around 20% of cases). Macroprolactin is routinely investigated using polyethylene glycol (PEG) precipitation in patients with elevated [prolactin].

4.5 Sources of error

There are a number of circulating isoforms of prolactin; the most common form is monomeric prolactin (little prolactin, 23kDa) comprising approximately 80% within the blood, however, dimeric prolactin ('big' prolactin, 48-56kDa) and polymeric prolactin ('big, big' prolactin, >100kDa) are also present. The dimeric and polymeric complexes have variable immunoreactivity and may be detected differently by individual immunoassays. The presence of a hook effect should be considered in patients with a large pituitary tumour and a mild elevation in serum [prolactin]; this can be investigated using serial dilution.

Immunoassays are susceptible to interference from heterophilic antibodies and this can be confirmed either by sample dilution or by the use of heterophile blocking tubes.

5 Reference intervals and variance

5.1.1 Reference interval (adults)

Male <400mU/L (Abbott ARCHITECT, method-dependent)

Female <630mU/L (Abbott ARCHITECT, method-dependent)

5.1.2 Reference intervals (others)

Pregnant female – up to 10-20x upper reference interval, gradually increasing throughout pregnancy

5.1.3 Extent of variation

5.1.3.1 Interindividual CV

27.0% serum/plasma (EFLM database)

5.1.3.2 Intraindividual CV

19.9% serum/plasma (EFLM database)

5.1.3.3 Index of individuality

0.73 serum/plasma

5.1.3.4 CV of method

Typically <3%

5.1.3.5 Critical difference

Approximately 53% (EFLM database)

5.1.4 Sources of variation

None

6 Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation

1. Investigation of symptoms consistent with hyperprolactinaemia e.g. galactorrhoea, amenorrhoea
2. Investigation of symptoms consistent with a pituitary tumour e.g. headache, visual field loss
3. Investigation of unexplained infertility in males and females
4. Secondary investigation in men with low testosterone levels

6.2 Confounding factors

Gender – [prolactin] is higher in females.

Pregnancy and lactation – marked increase in [prolactin]

7 Causes and investigation of abnormal values

7.1 High values

7.1.1 Causes

There are an extensive range of causes of elevated [prolactin]; examples are listed below.

Artefactual

- Macroprolactin

Physiological

- Pregnancy
- Breast feeding
- Stress
- Exercise

Drugs

- Dopamine antagonists e.g. methyl dopa
- Serotonin antagonists
- Antipsychotics e.g. phenothiazines, benzamides

Hypothalamic disease

- Tumours
- Inflammation

Pituitary disease

- Prolactinoma
- Other pituitary adenoma

Other

- Chest wall injury
- Hypothyroidism
- Chronic kidney disease
- Liver cirrhosis
- Anorexia
- Polycystic ovarian syndrome

7.1.2 Investigation

Investigation of hyperprolactinaemia should firstly rule out the presence of macroprolactin, of physiological states which increase [prolactin] and medication use. Hypothyroidism should also be excluded.

The higher the [prolactin], the greater the likelihood of prolactinoma. Microprolactinomas are associated with [prolactin] less than 4000 mU/L, while macroprolactinomas are associated with [prolactin] greater than 4000 mU/L. If a prolactinoma is suspected this should be investigated with imaging, e.g. pituitary MRI. [Prolactin] may also be raised by the mass effect of a pituitary tumour, resulting in pituitary stalk compression which impedes dopaminergic inhibition of prolactin release.

7.2 Low values

7.2.1 Causes

Low [prolactin] is not usually a concern in females or males, although it may result in an inability in females to lactate post-partum.

Severe deficiencies in prolactin may be associated with hypopituitarism.

7.2.2 Investigation

Low [prolactin] is not generally investigated, however, if hypopituitarism is suspected this should be investigated with appropriate endocrine tests and imaging.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

Limited data is available on the sensitivity and specificity of prolactin measurement as it is not generally used as a sole diagnostic test, but in combination with other investigations. One study (Kawaguchi *et al.* 2014, BMC Res Notes 7[555]) reported a sensitivity of 0.99 and specificity of 0.81 in distinguishing non-functional adenoma from prolactinoma. Another (Kyritsi *et al.* 2018, Eur J Clin Invest 48[7]) reported a sensitivity of 0.77 and specificity of 1.00 in identifying prolactinoma in patients with PCOS.

9 Systematic reviews and guidelines

9.1 Systematic reviews

1. Wang *et al.* (2012) Treatment of hyperprolactinaemia: a systematic review and meta-analysis. *Syst Rev* 1(33).

9.2 Guidelines

1. Melmed *et al.* (2011) Diagnosis and treatment of hyperprolactinaemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96(2):273-288.

2. NICE Clinical Guidance CG156 (2017) Fertility problems: assessment and treatment.
This recommends that prolactin should not be routinely measured in women with infertility unless they have an ovulatory disorder, galactorrhoea or a pituitary tumour.

9.3 Recommendations
None

10 Links

10.1 Related analytes
None

10.2 Related tests
None