# NATIONAL LABORATORY HANDBOOK

## Laboratory Testing for Hyperprolactinaemia (Prolactin)

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National Clinical & Integrated Care Programmes
Person-centred, co-ordinated care

PATHOLOGY

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

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### Background & Aetiology

Prolactin is a peptide hormone that is synthesised and secreted by the lactotrophic cells of the anterior pituitary, under the regulation of the hypothalamus. Prolactin's primary function is initiation and maintenance of lactation. However, its effect on gonadotrophin release means it also has effects on sex hormones, and fertility. Prolactin secretion is regulated by the inhibitory action of dopamine. When dopamine is prevented from acting on the D2 receptors of the lactotrophic cells (either physiologically, pathophysiologically including stress or pharmacologically), prolactin concentrations begin to rise, resulting in hyperprolactinaemia. Low levels of serum prolactin may indicate hypofunction of the pituitary gland.

### Scope

The aim of this guideline is to provide guidance on appropriate requesting of serum prolactin for use by clinicians and clinical laboratories. These guidelines apply to adult non-pregnant patients in hospitals and in primary care settings in the Republic of Ireland.

### Key recommendations for Clinical Users

- All requests must be supported by adequate and relevant clinical details.
- A single prolactin measurement in serum, preferably taken 3-4 hours after waking, can determine hyperprolactinaemia.
- Stress is a recognised cause of mild hyperprolactinaemia and under these circumstances repeated blood sampling, taken through an indwelling cannula over an hour will demonstrate a fall, invariably to levels expected in health.
- Hyperprolactinaemia may be the result of macro forms of prolactin known as macroprolactin. This non-bioactive prolactin isoform should be excluded in clinically

asymptomatic patients with biochemical hyperprolactinaemia, before requesting imaging or other investigations[1].

- Many commonly used drugs, including the oral contraceptive pill, may cause hyperprolactinaemia.

- Various commercially available assays for prolactin are currently in use in Ireland. Reports from different labs will differ in reference intervals, units of concentration and cross reactivity with macroprolactin.

## Key recommendations for Laboratories

### *Macroprolactin*

- Laboratories should test for macroprolactinaemia in all samples with a raised prolactin, to exclude macroprolactinaemia.
- PEG precipitation of samples is a relatively quick and inexpensive method of testing for macroprolactin.
- Laboratories should establish a PEG treated reference interval to aid interpretation.

### *Hook Effect*

- If an unexpectedly low/normal prolactin result is obtained on a patient with a prolactinoma, serial dilution of the serum sample can aid in identifying the hook effect.

### *Reporting*

- Prolactin results should be interpreted in relation to gender-specific reference intervals.
- Prolactin methodology and traceability should be stated on the laboratory report.

## Testing

## Who to Test

Prolactin testing may be used to investigate signs and symptoms of hyperprolactinaemia: galactorrhoea; amenorrhoea/oligomenorrhoea and/or infertility in women; infertility and/or erectile dysfunction in men.

Prolactin testing is useful in detecting and diagnosing prolactin producing pituitary adenomas (prolactinoma) as well as aiding in monitoring tumour progression, response to treatment and reoccurrence. Prolactin may be ordered if clinical signs and symptoms of pituitary adenoma (headache, visual field defects) are present.

Prolactin measurement, along with other pituitary hormones, may be useful in assessing hypothalamic/pituitary function.

| | Description of Group | Clinical Indications |
|---|---|---|
| **Group1** | Fertility | Galactorrhoea (male or female),<br>Amenorrhoea,<br>Oligomenorrhoea,<br>Infertility (male or female),<br>Loss of libido (male or female). |
| **Group 2** | Pituitary Adenoma<br>(Prolactinoma or compressive) | Headache, visual field defect.<br>Pituitary adenoma visible on CT/MRI. |
| **Group 3** | Hypothalamic/Pituitary Dysfunction | Pituitary stalk damage or resection,<br>Hypopituitarism,<br>Granuloma/infiltrative diseases of the hypothalamus/pituitary. |

**Table 1. Indications for measurement of Prolactin***

* Signs, symptoms and causality can overlap. Lists not exhaustive.

## Who Not to Test

The Endocrine Society recommends serum prolactin measurements are not carried out in pregnant patients with prolactinomas [(1).]

Do not include in “Routine Bloods”, health-screening requests, or in the absence of relevant symptoms (see above).

## Factors to exclude and consider

Macroprolactin is an inactive form of prolactin that can be present in up to 26% of samples with raised prolactin. It is important to further test samples with raised prolactin levels, to estimate the quantity of macroprolactin contributing to the prolactin result. Prolactin may be raised in a number of physiological states: Pregnancy; breast-feeding; exercise; sleep; stress (including stress of venepuncture) and eating protein rich meals.

The most frequent cause of non-tumoural hyperprolactinaemia is medications[(1).] In particular, neuroleptics and anti-psychotic drugs can cause an elevated prolactin (e.g. 50-100% of patients taking respiradone have hyperprolactinaemia [(2,3)]). Many other medications such as the oral contraceptive pill, anaesthetics, antihypertensives, antihistamines (H2), anticonvulsants, antidepressants, cholinergic agonists, dopamine receptor blockers, dopamine synthesis inhibitors among others, can also cause elevated serum prolactin concentrations.

Conditions such as renal failure, primary hypothyroidism, adrenal insufficiency and polycystic ovary syndrome have been implicated in causing elevated serum prolactin concentrations.

## Who to Re-Test

If elevated prolactin is reported in an asymptomatic patient, it may be due to stressful venepuncture, a repeat sample may be taken a few days later. In female patients, repeat sampling in the early follicular phase (onset of menses to day 5) of the menstrual cycle ensuring stress free venepuncture, is preferable [4].

Further investigation is required when prolactin levels exceed the upper reference interval on at least two occasions, when medications and physiological causes are excluded, and where stress has been avoided [5].

## Specimen and ordering information

All requests (electronic and paper) and specimens must adhere to the laboratories standard requirements stated in the Laboratory User Guide. Test requests must contain all necessary demographics and should provide the indication for testing together with the relevant clinical information, medication details (prescribed and over the counter), date and time of venepuncture, to enable accurate result interpretation. In order to comply with accreditation standards (ISO: 15189:2012), laboratories cannot accept or process samples that do not meet their defined minimum standards.

Provide any relevant clinical details (pregnancy, medications etc.) on request. A single serum/plasma sample (no specific patient preparation required) should be sufficient to identify hypo- or hyperprolactinaemia. Ideally samples for prolactin should be taken at their physiological peak, 3-4 hours after waking [6] however, samples may be taken at any time of day. Avoid excess stress at venepuncture.

Samples should be centrifuged and separated from cells on receipt. Prolactin is stable in separated serum/plasma for 6 days at 4-6°C [7].

## How to Test

Most endocrine laboratories in Ireland (and the UK) use two-site (sandwich) immunoassays for analysis of serum prolactin [8]. Differences in the various commercial assays, means that prolactin results can vary from laboratory to laboratory. Prolactin results should be interpreted in the context of locally derived reference interval. Normal prolactin values are higher in women than in men, hence the use of gender-specific reference intervals is recommended.

The various methods available for measurement of prolactin, also vary in their cross reactivity with macroprolactin [9]. Clinicians and laboratory scientists need to be familiar with the assay method used in their laboratory and the degree to which macroprolactin impacts prolactin results.

In order to assess whether a patient's prolactin level remains elevated when macroprolactin has been precipitated and removed, it is advisable to establish a post-PEG treated reference interval (i.e. prolactin concentrations in post-PEG precipitated normoprolactinaemic sera) specific to the local method [10].

Macroprolactinaemia (where the majority of prolactin present is bio-inactive) has been observed in 10-26% of all hyperprolactinaemic samples identified in clinical laboratories [11]. Therefore, it is advisable that laboratories add macroprolactin testing on to all samples with elevated prolactin concentrations. This may be done as a reflex software rule or reflective testing at the point of clinically validating results.

If macroprolactin is determined to be the predominant form of prolactin in circulation, it may not be necessary to assess macroprolactin on subsequent prolactin measurements. Studies suggest that repeat measurement of macroprolactin is not necessary, since the condition persists over time and macroprolactin concentration will rise and fall relative to total prolactin concentration [(11)].

Patients with prolactinoma often have serum prolactin concentrations in the thousands of mIU/L. Prolactin of this concentration can overwhelm the available binding sites in two site (sandwich) immunoassays, giving a falsely low prolactin result - a phenomenon known as the hook effect [(4)]. If an unexpectedly low/normal prolactin result is obtained on a patient with a prolactinoma, serial dilution of the serum sample can aid in identifying the hook effect.

## Interpretation of tests

See previous section - *Factors to exclude & consider*

Laboratory specific reference ranges should be available on the test report, or available on consultation of the Laboratory User Manual.

If the sample was further tested for the presence of macroprolactin, a post-PEG precipitation prolactin value that falls within the PEG-treated reference interval indicates that the majority of prolactin present is macroprolactin. Macroprolactin has no bioactivity, and no clinical significance.

In general, expected prolactin concentrations in health are approximately 80-300 mU/L (4-14 µg/L) in men and 100-550 mU/L (5-26 µg/L) in women (please see local laboratory gender-specific reference intervals).

Prolactin levels are typically less than 4,000 mU/L and invariably higher than 2,000 mU/L in patients with a microprolactinoma. Levels in excess of 6,000 mU/L suggest the presence of a macroprolactinoma [(4)].

## Information for patients

Prolactin is a hormone secreted by the pituitary gland. Its main role is to control milk production by breast tissue. The level of prolactin in your blood can be affected by a number of medicines, so it is important to tell your doctor about all medicines that you are taking, even if these are not on prescription. Prolactin levels can be raised if you are stressed (even if you are nervous about having your blood taken), following exercise, and even after eating a protein rich meal.

Excess production of prolactin can cause unexpected milk production from breast tissue, subfertility, in women irregular or no periods, and in men erectile dysfunction. Occasionally there will be other signs of possible pituitary disease which may lead your doctor to measure your prolactin level.

If there is a raised level of prolactin found in your blood, the lab needs to do further tests to see if this is active or inactive prolactin. Inactive prolactin is the cause of a raised prolactin in about a quarter of people – this form of prolactin is not associated with disease. If you have a raised level of the active form of prolactin, this will usually be repeated after making sure that stress and other simple factors which can cause a raised prolactin have been controlled. If the prolactin continues to be elevated, you may be referred to an endocrinologist for further investigation of your symptoms.

It is very hard to interpret prolactin measurements when you are pregnant or breast feeding, and it is unlikely that the test will be done at this time, apart from in some very specialised situations.

## Consultation Plan and History

The guideline was drafted by the authors. Initial consultation with the Chemical Pathology Working Group of the National Clinical Programme for Pathology was completed, following which the guideline was submitted to the Irish Endocrine Society.

After initial expert review the guideline was submitted for full consultation, including Fellows of the Royal College of Physicians in Ireland and the ICGP.

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