

Guidelines for Ordering Serum Levels of Gonadotropins (FSH, LH) and Prolactin CLP-021

Revised June, 2008

(Replaces October 2000 version)

1. Scope

This laboratory Guideline is intended to assist community clinicians in determining the indications for ordering serum levels of Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH) and/or Prolactin.

This Guideline will be applicable in most, but not all clinical situations. It cannot serve as a substitute for sound clinical judgment. Complex endocrinological problems will generally require referral of the patient to an appropriate specialist.

2. Background

FSH and LH (gonadotropins) are produced by the pituitary gland. They (especially LH) are released in a pulsatile fashion in response to the pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH). In women, the pulse frequency (generally occurring as often as every 60-90 minutes, but may be as few as 2-3 per day) and amplitude vary during different phases of the menstrual cycle. This is reflected in varying serum gonadotropin levels, not only within the phases of the menstrual cycle itself but even within a single day.

Gonadotropin-releasing hormone (GnRH) is synthesized in the hypothalamus. It stimulates FSH and LH release from the pituitary gland. Sex hormones, predominantly estradiol, generally inhibit both gonadotropin and GnRH secretion via a negative feedback loop. In addition to the sex hormones, at least two other gonadal hormones, activin and inhibin, selectively activate and inhibit pituitary FSH secretion.

Prolactin, also an anterior pituitary hormone, is secreted as a prohormone and subsequently cleaved to its mature, active form. Episodic release of prolactin causes serum levels of prolactin to follow a circadian/ultradian (recurrent cycles throughout a 24 hour period) rhythm.

In contrast to other anterior pituitary hormones, the predominant hypothalamic control over prolactin secretion is inhibitory, mediated by the neurotransmitter/neurohormone dopamine. The stimulatory signal for prolactin release is mediated (under some conditions) by thyrotropin releasing hormone, and possibly by oxytocin, vasoactive intestinal peptide and a host of other endogenous neurohormones and neurotransmitters as well. During pregnancy, estrogens appear to exert some degree of positive control over prolactin synthesis and secretion.

3. Hormone Function

FSH

In women, FSH is the predominant circulating gonadotropin prior to puberty as well as after menopause. Its function during the ovulatory cycle is to stimulate the development of ovarian follicles and selection of the dominant follicle during the follicular phase of the cycle.

In men, FSH stimulates seminiferous tubular function, leading to sperm production.

LH

In women, the mid-cycle LH secretory spike is induced (positive feedback) by increased estradiol secretion from the dominant follicle. This LH surge initiates the final maturation of the dominant follicle, and induces rupture of the ovarian follicle, extrusion of the ovum, and luteinization of the follicle to form the corpus luteum. Subsequently, progesterone secretion from the corpus luteum acts on the estrogen-primed endometrium to induce the changes necessary to make the endometrium receptive to implantation of an embryo.

In men, LH stimulates testosterone production by the Leydig cells in the testes.

Prolactin

In women, the function of prolactin is to stimulate milk production in the estrogen-primed breast. Serum prolactin levels increase during pregnancy and suckling. Prolactin also suppresses gonadotropin production, e.g. during breast feeding.

In men, the function of prolactin is generally unknown. However, elevated prolactin levels are known to suppress gonadotropin production and libido, which often results in clinical hypogonadism, low serum testosterone levels and a low sperm count.

4. Laboratory Investigation

Clinicians are reminded to provide relevant clinical information, especially menstrual dates, when requesting serum FSH, LH and/or prolactin levels.

(a) Women

In women, FSH is often requested in conjunction with other tests (such as LH, testosterone, estradiol, and progesterone) in the assessment of infertility. FSH levels are useful in the investigation of menstrual irregularities and to aid in the diagnosis of pituitary disorders or diseases involving the ovaries.

Primary Amenorrhea

Gonadotropin measurements help to distinguish an ovarian cause of amenorrhea (e.g. Turner's syndrome) from a hypothalamo-pituitary cause (e.g. pituitary lesions, Kallman's syndrome).

In primary ovarian failure, estrogen concentrations are very low. This results in a lack of negative feedback on the pituitary and thus elevated FSH and LH levels. In hypothalamo-pituitary dysfunction however, serum gonadotropin as well as estrogen concentrations are low. There can be numerous causes for this and dynamic testing of pituitary and hypothalamic function is often appropriate.

Secondary Amenorrhea

The commonest cause of secondary amenorrhea is pregnancy - ruled out by measuring serum β -hCG.

In the absence of pregnancy, serum gonadotropin levels will help distinguish between ovarian failure (e.g. menopause), and estrogen deficiency due to hypothalamo-pituitary causes. FSH levels are often elevated for 2 to 3 years before menses cease because of increasing ovarian resistance to gonadotropins during perimenopause. Other causes of secondary amenorrhea may include:

- Polycystic Ovary Syndrome (hyperandrogenic anovulation) - see #5 next page
- Hyperprolactinemia
- Anorexia/Bulimia
- Stress and psychological disorders

- Acute and chronic systemic illnesses
- Pituitary Tumors
- Thyroid Dysfunction

With the approach of natural menopause and the beginning of ovarian failure of any cause, serum FSH levels increase.

Here as well, imaging and dynamic pituitary testing may be necessary to distinguish different causes for low serum gonadotropin levels.

(b) Men

Serum FSH, LH and/or prolactin levels may be requested in cases of hypogonadism/suspected gonadal failure, low sperm count, testicular feminization syndrome and/or testicular dysfunction. These hormone levels are also of value in ruling out pituitary or hypothalamic failure, as discussed above.

5. The Polycystic Ovary Syndrome (PCOS)

The diagnosis of PCOS is commonly made in young women with irregular or infrequent menses. These patients typically present with evidence of hyperandrogenism with hirsutism, acne and oily skin. A large proportion of these patients are overweight. Infertility is a common presenting complaint. Increased prevalence of PCOS as well as metabolic syndrome in other family members is common. The underlying mechanism in a large proportion of these patients is hyperinsulinemia, usually secondary to selective insulin resistance. The increased insulin level is thought to have a direct effect on the ovaries, causing disturbances in normal hormone output and follicular development.

Evidence of elevated androgen/androgen precursors (testosterone, DHEA-S) is sometimes found. About 20% of the patients have a mild hyperprolactinemia - typically less than 40 ug/L.

The differential diagnosis includes other causes of hyperandrogenism and amenorrhea, such as late-onset congenital adrenal hyperplasia, androgen-secreting ovarian or adrenal lesions or pituitary tumours.

Paradoxically, ultrasonic identification of polycystic ovaries is not required for the diagnosis to be made.

6. Hyperprolactinemia

In women, the most common reasons for measuring prolactin levels are:

- Infrequent menses/amenorrhea
- Infertility
- Galactorrhea

Elevated serum prolactin levels may cause infertility due to a disruption of regular ovulation. Clinically, this can present as irregular cycles or as secondary amenorrhea.

Note: (a) It is important not to do a breast examination for at least an hour before drawing blood for measurement of prolactin, as this may raise the prolactin level and (b) elevated serum prolactin levels should be confirmed with a repeat test on a fresh blood sample drawn after an overnight fast.

In men, the most common reasons for measuring serum prolactin are erectile dysfunction, lack of libido or gynecomastia. In men with hyperprolactinemia, serum gonadotropins and testosterone levels are usually low and there is often an accompanying diminished sperm count.

In both sexes, the most common causes of elevated prolactin levels are:

- Pituitary prolactin secreting adenomas (prolactinomas)
- Drugs e.g. dopamine antagonists such as Domperidone; opiates; psychotropic medications, especially phenothiazines
- Hypothyroidism (serum TSH may be used to rule out primary hypothyroidism as a cause of hyperprolactinemia)
- Note that transient increases in serum prolactin levels can be caused by sleep, exercise and hyperglycemia

7. Additional Notes

Serum LH is rarely useful on its own. In the Polycystic Ovarian Syndrome (PCOS), the LH/FSH ratio is commonly raised, but this ratio is non-diagnostic.

Elevated serum FSH levels are very rarely due to FSH-secreting pituitary tumors. In such cases, however, the elevated FSH level will be associated with a low or normal serum level of LH. Sexual function will be variably affected.

Mildly elevated prolactin levels (e.g. less than about 40ug/L) are non-diagnostic and only rarely indicate pituitary lesions. Elevated serum levels of prolactin should always be confirmed with repeat testing.

Prolactin-immunoglobulin complexes (termed 'macroprolactin'), which have little or no biological activity, are occasionally found in human serum. These complexes are too large to be cleared by the kidneys and consequently accumulate, causing anomalous elevations in the serum prolactin level when measured with certain immunoassays ('macroprolactinemia'). Macroprolactinemia should always be considered when elevated serum levels of prolactin are reported in patients who do not display the usual clinical symptoms of hyperprolactinemia. Many laboratories routinely perform testing to exclude macroprolactinemia as the cause of an elevated serum prolactin level. When such testing has been performed, it will be duly noted on the laboratory report. In some laboratories, testing to rule out macroprolactinemia may need to be specifically requested.

8. References:

Toward Optimized Practice (TOP) Program, Alberta Medical Association, Alberta Health and Wellness, the College of Physicians and Surgeons, and Alberta's Health Regions. Laboratory Endocrine Testing Guidelines: Investigation of Amenorrhea (Without Hirsutism) and Menopause; Reviewed 2008

Toward Optimized Practice (TOP) Program, Alberta Medical Association, Alberta Health and Wellness, the College of Physicians and Surgeons, and Alberta's Health Regions. Laboratory Endocrine Testing Guidelines: Investigation of Gonadal Disorders: Hirsutism; Reviewed 2008

Backer, L.C., Rubin, C.S., Marcus, M., Kieszak, S.M., Schober, S.E. Serum Follicle-Stimulating Hormone and Luteinizing Hormone Levels in Women Aged 35-60 in the US Population: the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), Centers for Disease Control and Prevention, Atlanta, GA, USA

Burger, H.G. The Endocrinology of the Menopause. Prince Harry's Institute of Medical Research, Clayton, Victoria, Australia, Maturitas 1996; 23(2):129-136

Pincus, S.M., Veldhuis, J.D., Mulligan, T., Iranmanesh, A., Evans, W.S. Effects of Age on the Irregularity of LH and FSH Serum Concentrations in Women and Men. Department of Internal Medicine, University of Virginia, Am J Physiol 1997; 273:1989-1995

Rittmaster, R.S. Hyperandrogenism. What is Normal? N Engl J Med 1997; 327:194-195

Serri, O., Chik, C. L., Ur, E. Ezzat, S. Diagnosis and management of hyperprolactinemia. Can Med Assoc J 2003; 169(6):575-581

Smellie, W. Cases in Primary Care Laboratory Medicine: Testing pitfalls and summary of guidance on sex hormone testing. Brit Med J 2007; 334:91-94.

Acknowledgements

The OAML gratefully acknowledges the contributions of our expert panel members:

William Singer MD, BS, FRCPC, FRCPE, FACP
Associate Professor of Medicine and Laboratory
Medicine, University of Toronto
Consultant Physician, Division of Endocrinology &
Metabolism, St. Michael's Hospital, Toronto
Consultant, LMC Endocrinology Centre, Toronto

Ellen M Greenblatt, MD, FRCSC
Clinical Director, Reproductive Biology and IVF Units,
Division of Reproductive Sciences,
RE&I Fellowship Programme Director
Department of Obstetrics and Gynaecology,
Mount Sinai Hospital,
Associate Professor, University of Toronto

Laboratory Guidelines in Support of Clinical Practice

The OAML, through its Quality Assurance Committee, co-ordinates the development, dissemination, implementation and review of Guidelines for Clinical Laboratory Practice.

Guidelines are reviewed every 5 years, or as the literature warrants. When consensus on the Guideline is achieved by the Committee, the Guideline is submitted to the OAML's Board of Directors for approval before distribution to clinicians.

The comments of end users are essential to the development of Guidelines. You are strongly encouraged to submit your comments on this or any other OAML Guideline to:

Chair
Quality Assurance Committee
Ontario Association of Medical Laboratories
5160 Yonge Street, Suite 710
North York, Ontario
M2N 6L9

Tel: (416) 250-8555
Fax: (416) 250-8464
E-mail: oaml@oaml.com
Internet: www.oaml.com

Quality Assurance Committee Members

Frank Thompson MD, FRCPC
Medical Director, LifeLabs[®], Ontario

Philip Stuart MD, PhD, FRCP(C)
Medical Director, CML HealthCare Inc.

Joel Goodman PhD, FCACB
VP, Strategies and Innovation
Gamma-Dynacare Medical Laboratories

Janice Nolan MLT, CQA (ASQ)
Director, Quality & Regulatory Affairs
LifeLabs[®]

Chair

Judy Ash BSc, ART, CQMgr, CQA (ASQ)
Director, Programs & Member Services
Ontario Association of Medical Laboratories

No conflicts of interest declared

Warning & Disclaimer

This Guideline was prepared to assist clinicians who order tests from community laboratories. Users must ensure that their own practices comply with all specific government policies and specific legislative and accreditation requirements that apply to their organizations. The Guideline is not meant to be construed as legal advice or be all inclusive on this topic. Given the complexity of legal requirements, users are reminded that whenever there is uncertainty regarding whether some aspect of a Guideline is appropriate for their practice or organization, further direction should be obtained from the Laboratory Director, their own professional association, college and/or legal counsel or appropriate government ministry.

ONTARIO ASSOCIATION OF MEDICAL LABORATORIES

WORKING TO KEEP OUR HEALTH CARE SYSTEM HEALTHY™

 OAML

OAML 