



BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: My patient has elevated prolactin and infertility, but normal periods and a negative pituitary study. What should I do?

ISRAEL B. ORIJA, MD

Department of Endocrinology, Diabetes, and Metabolism,
The Cleveland Clinic Foundation

CHARLES FAIMAN, MD

Department of Endocrinology, Diabetes, and Metabolism,
The Cleveland Clinic Foundation

A: When a woman of childbearing age has elevated serum prolactin levels but does not have amenorrhea, galactorrhea, or infertility, we should consider a diagnosis of *macroprolactinemia* before embarking on a series of potentially unnecessary and expensive tests and treatments.

■ SEVERAL TYPES OF PROLACTIN

Why might a patient not have symptoms despite modest hyperprolactinemia?

Prolactin may be present in the circulation in a number of forms: a 23-kD monomer, small aggregates, or as macroprolactin, a large aggregate usually associated with immunoglobulin G.^{1,2}

In healthy people and in patients with prolactinomas, “small” (monomeric) prolactin accounts for 80% to 90% of circulating prolactin.³ Persistent elevations of monomeric prolactin cause infertility, amenorrhea, and galactorrhea. An extensive workup and drug therapy are often required to determine the cause and return levels to normal.

Macroprolactinemia is usually asymptomatic

Immunoassay studies show that macroprolactin is the predominant form of prolactin in 10% to 25% of hyperprolactinemic blood samples. Macroprolactinemia may be present in about 0.2% of the general population.⁴⁻⁶

Macroprolactinemia typically is asympto-

matic, as the large size of the macroprolactin molecule may prevent it from binding to cellular prolactin receptors. On the other hand, macroprolactinemia has been reported in patients with menstrual dysfunction, and it can also be present in some patients with a pituitary adenoma.

Macroprolactinemia can be detected by gel filtration chromatography, a method not available in commercial laboratories. Polyethylene glycol, commonly used in the laboratory to precipitate proteins, has been used effectively to detect macroprolactinemia,^{7,8} and some have suggested that laboratories screen all hyperprolactinemic samples with this reagent. However, these tests are not readily available, so we recommend that patients with hyperprolactinemia be considered for an endocrine referral.

Although a pituitary study, preferably magnetic resonance imaging, is mandatory in patients with persistent hyperprolactinemia, it is not necessary in patients with a diagnosis of macroprolactinemia.

Patients with macroprolactinemia often respond poorly to dopaminergic agonist therapy used to lower prolactin levels.

■ PREVALENCE OF HYPERPROLACTINEMIA

Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic-pituitary axis. It is more commonly diagnosed in women than in men, and, if it persists, it usually causes infertility, amenorrhea, and galactorrhea.

The prevalence of hyperprolactinemia varies: about 0.2% in an unselected normal adult population, 5% in men who present with impotence or infertility, 5% in a family

Prolactin comes in different sizes

TABLE 1**Causes of hyperprolactinemia****Physiologic causes**

- Pregnancy
- Nursing
- Nipple stimulation
- Sexual intercourse
- Stress (surgery, hypoglycemia, myocardial infarction, syncope, trauma, venesection)
- Sleep
- Exercise
- Food ingestion

Pharmacologic causes

- Dopamine receptor antagonists
- Antipsychotics
 - Phenothiazines
 - Butyrophenones
 - Thioxanthenes
 - Risperidone
 - Sulpiride
- Antiemetics
 - Metoclopramide
 - Domperidone
- Dopamine-depleting agents
 - Methyldopa
 - Reserpine
- Antidepressants
 - Tricyclic antidepressants
 - Selective serotonin receptor inhibitors
- Hormones
 - Estrogens (high-dose)
 - Antiandrogens
- Opiates
- Verapamil
- Cimetidine (intravenous)

Pathologic causes

- Pituitary disease
 - Prolactinomas
 - Mixed growth hormone/prolactin- or adrenocorticotrophic hormone/prolactin-secreting adenomas
 - Intrasellar/perisellar tumors causing stalk compression (nonsecretory adenoma, germinoma, meningioma, craniopharyngioma, hamartoma, glioma, metastasis)
 - Intrasellar cyst
 - Rathke cleft cyst
 - Hypothalamic and pituitary stalk disease
 - Granulomatous diseases (sarcoidosis, tuberculosis, eosinophilic granuloma)
 - Cranial irradiation
 - Pituitary stalk section
 - Empty sella (uncommon)
 - Vascular (aneurysm, arteriovenous malformation)
 - Lymphocytic hypophysitis
- Primary hypothyroidism
- Chronic renal failure
- Cirrhosis
- Chest wall trauma (including surgery, herpes zoster)
- Seizures, electroconvulsive therapy
- Polycystic ovarian syndrome
- Ectopic secretion of prolactin (extremely rare)

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planning clinic population, and up to 17% in women with reproductive disorders.⁹⁻¹¹ Prolactinomas account for 25% to 30% of functioning pituitary tumors and are the most frequent cause of persistent hyperprolactinemia.⁹ Other causes must be excluded (TABLE 1).

■ APPROACH TO HYPERPROLACTINEMIA

A history, physical examination, and pregnancy test are crucial. Women with hyperprolactinemia may present with classic symptoms of menstrual dysfunction (oligomenorrhea, amenorrhea) with or without galactorrhea and infertility; approximately 75% of patients presenting with galactorrhea and amenorrhea have hyperprolactinemia. Hyperprolactinemia may also be associated with features of hyperandrogenism such as hirsutism and acne.

On the other hand, the effects of hyperprolactinemia may be more subtle. Menses may be regular but with anovulatory cycles or luteal phase insufficiency and resultant infertility.

Men may present with loss of libido, infertility, gynecomastia, galactorrhea, or erectile dysfunction. Since there is no early warning signal of "menstrual dysfunction" in men, they are more likely to present with mass effects related to the presence of an intracranial tumor, such as headaches and visual disturbances.

Loss of bone mass is a feature of persistent hyperprolactinemia in either sex, usually associated with prolonged hypogonadism.^{9,10}

■ REFERENCES

1. Bonhoff A, Vuille JC, Gomez F, Gellersen B. Identification of macroprolactin in a patient with asymptomatic hyperprolactinemia as a stable PRL-IgG complex. *Exp Clin Endocrinol Diabetes* 1995; 103:252-255.
2. Hattori N. The frequency of macroprolactinemia in pregnant women and the heterogeneity of its etiologies. *J Clin Endocrinol Metab* 1996; 81:586-590.
3. Suh HK, Frantz AG. Size heterogeneity of human prolactin in plasma and pituitary extracts. *J Clin Endocrinol Metab* 1974; 39:928-935.
4. Bjoro T, Morkrid L, Wergeland R, et al. Frequency of hyperprolactinemia due to large molecular weight prolactin (150-170 kD PRL). *Scand J Clin Lab Invest* 1995; 55:139-147.
5. Leslie H, Courtney CH, Bell PM, et al. Laboratory and clinical experience in 55 patients with macroprolactinemia identified by a simple polyethylene glycol precipitation method. *J Clin Endocrinol Metab* 2001; 86:2743-2746.
6. Vallette-Kasic S, Morange-Ramos I, Selim A, et al. Macroprolactinemia revisited: a study on 106 patients. *J Clin Endocrinol Metab* 2002; 87:581-588.
7. Vieira JG, Tachibana TT, Obara LH, Maciel RM. Extensive experience and validation of polyethylene glycol precipitation as a screening method for macroprolactinemia. *Clin Chem* 1998; 44:1758-1759.
8. Fahie-Wilson MN. Polyethylene glycol precipitation as a screening method for macroprolactinemia. *Clin Chem* 1999; 45:436-437.
9. Mah PM, Webster J. Hyperprolactinemia: etiology, diagnosis, and management. *Semin Reprod Med* 2002; 20:365-374.
10. Luciano AA. Clinical presentation of hyperprolactinemia. *J Reprod Med* 1999; 44(suppl):1085-1090.
11. Biller BM. Diagnostic evaluation of hyperprolactinemia. *J Reprod Med* 1999; 44(suppl):1095-1099.

ADDRESS: Israel B. Orija, MD, Department of Endocrinology, Diabetes, and Metabolism, A53, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, or Charles Faiman, MD, Department of Endocrinology, Diabetes, and Metabolism, A53, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

Confirm that the prolactin elevation is persistent

The general approach to the workup is to confirm persistent hyperprolactinemia. Since prolactin secretion responds to stress and to breast and genital stimuli, it is important not to repeat prolactin testing immediately after a breast or pelvic examination or a difficult venipuncture.

Persistent hyperprolactinemia demands a diligent search for obvious reversible causes (TABLE 1). Magnetic resonance imaging of the pituitary gland is generally recommended and should be done even with a modest prolactin elevation. A large space-occupying lesion can compress the pituitary stalk, leading to disruption of the tonic hypothalamic inhibition of prolactin secretion and consequent modest hyperprolactinemia.

■ TREATMENT

Elevated prolactin may abate when treatment with an offending drug is stopped or an underlying disorder such as hypothyroidism is treated.

Hypothyroidism deserves special mention. Primary hypothyroidism is a recognized cause of hyperprolactinemia associated with pituitary enlargement, sometimes mimicking a tumor, which resolves with thyroxine replacement.

Dopaminergic agonists such as bromocriptine or cabergoline can relieve the symptoms of symptomatic hyperprolactinemia. ■

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