Hyperprolactinemia: The ABCs of diagnosis and management

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners and other healthcare providers who provide primary care for women.

CE approval period: Now through December 31, 2022

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit including 0.25 contact hours of pharmacology content

Goal statement: Nurse practitioners and other healthcare providers who provide primary care for women will increase their knowledge about signs and symptoms, causes, assessment, and medical management of hyperprolactinemia.

Needs assessment: A thorough understanding of gynecologic endocrinology including the potential impact of alterations in hormone levels within the hypothalamic-pituitary-ovarian axis is needed for nurse practitioners and other healthcare providers who provide primary care for women. This is evident when increases in anterior pituitary gland secretion of the hormone prolactin result in menstrual disorders, infertility, and other endocrine-related manifestations. Knowledge for appropriate assessment and management is crucial to address these manifestations.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Describe common causes for and clinical manifestations of hyperprolactinemia.
2. Discuss components of assessment to include history, physical examination, and laboratory and diagnostic studies.
3. Describe indications, mechanism of action, efficacy, adverse effects, and contraindications for pharmacologic options in treating hyperprolactinemia.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH) and has been approved for 1 contact hour of CE credit, including 0.25 hours of pharmacology content.

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William E. Somerall, Jr, MD, MAEd, has no actual or potential conflicts of interest in relation to the contents of this article. **D'Ann W. Somerall, DNP, MAEd, CRNP, FNP-BC, FAANP,** has no actual or potential conflicts of interest in relation to the contents of this article.

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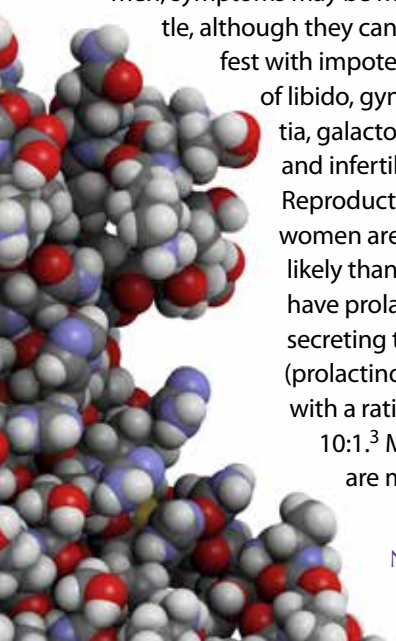
Hyperprolactinemia frequently presents with signs and symptoms of hypogonadism with resulting irregular menses, amenorrhea, infertility, and galactorrhea. This article reviews the physiologic and pathophysiologic causes of hyperprolactinemia. Manifestations of hyperprolactinemia, important lab and imaging studies, and medical treatment are described.

KEY WORDS: **prolactin, hyperprolactinemia, pituitary adenoma, prolactinoma, hypogonadism, galactorrhea**

Hyperprolactinemia, an increase in circulating prolactin levels, has variable physiologic, pathologic, and drug-induced causes.[1] It is most frequently identified in premenopausal women because of its association with anovulation, irregular menses, infertility, and breast discharge. In men, symptoms may be more subtle, although they can manifest with impotence, loss of libido, gynecomastia, galactorrhea, and infertility.[2] Reproductive-age women are more likely than men to have prolactin-secreting tumors (prolactinomas) with a ratio of 10:1.[3] Men are more frequently diagnosed with macroprolactinomas (tumors > 2 cm in diameter) compared with women who are more commonly diagnosed with microprolactinomas (tumors < 1 cm in diameter).[2] Nurse practitioners who provide primary women's healthcare and/or who provide infertility care for women and men will see patients with hyperprolactinemia in their clinical practice. NPs in primary women's healthcare settings should be able to identify signs and symptoms of hyperprolactinemia, conduct an initial assessment, and collaborate and/or make appropriate referrals in the diagnostic workup and management for this condition. The purpose of this article is to describe the causes, manifestations, diagnosis, and management strategies for women with hyperprolactinemia.



Physiologic causes of hyperprolactinemia

Prolactin (PRL) is produced and secreted by lactotrophs, which comprise about 20% of the anterior pituitary gland. Normally, dopamine and thyroxin inhibit the secretion of PRL while thyrotropin-releasing hormone (TRH) and adrenocorticotrophic hormone (ACTH) stimulate release of PRL.[1,4] Estrogen improves PRL secretion by inhibiting the effects of dopamine and enhancing the effects of TRH.[1]

Increasing estrogen levels during pregnancy induce lactotroph hyperplasia resulting in maximum PRL levels at the time of giving birth.[1] The primary purpose of increasing PRL levels is to stimulate the glandular breast tissue for subsequent breast milk production and lactation maintenance.[1,4] During pregnancy, PRL levels steadily increase to approximately 200 ng/mL in the third trimester but values can range up to 400 ng/mL. Serum PRL will return to normal prepregnancy levels 2 to 3 weeks postpartum if not breastfeeding. With breastfeeding, PRL levels increase depending on intensity of nipple stimulation. Even with continued breastfeeding, PRL levels will return to prepregnancy levels by approximately 6 months postpartum.[1]

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levels. This is believed to be in response to changes in the autonomic nervous system and the increased release of ACTH. This response in women is greater than in men, however, due to the effects of estrogen.[4] Other physiologic causes of increased PRL release include nipple stimulation, chest wall stimulation, meals, general anesthesia, exercise, and sexual activity.[4]

Pathologic causes of hyperprolactinemia

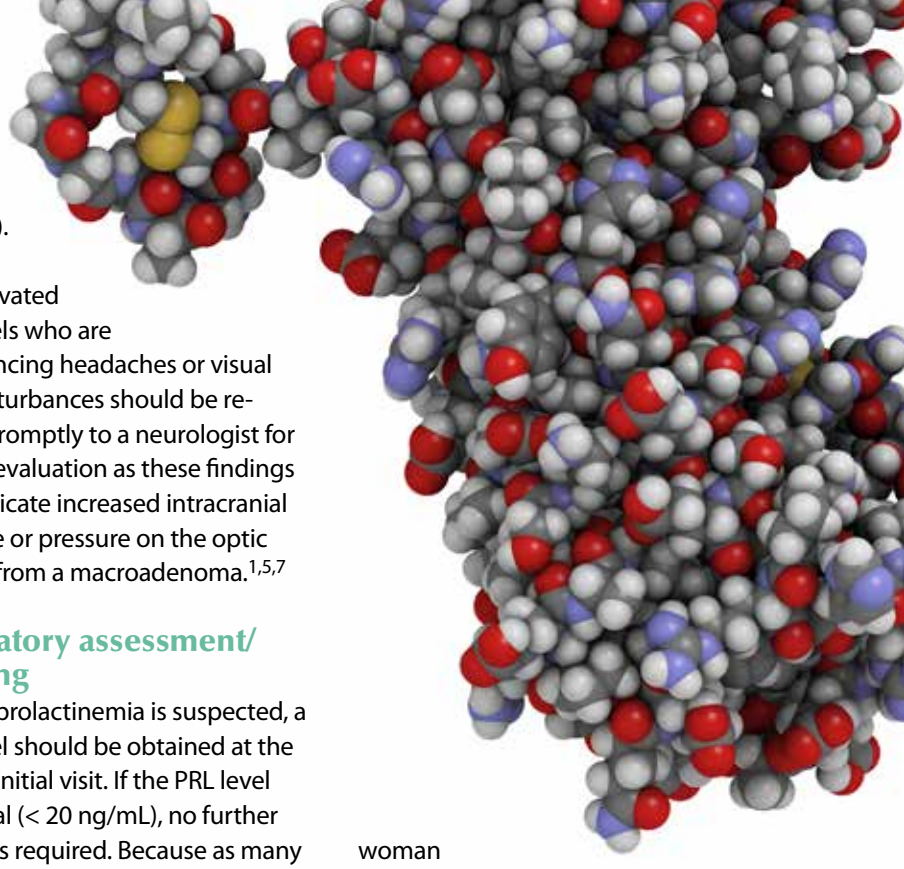
The most common pathologic cause of hyperprolactinemia is a prolactin-secreting adenoma.[1,5] In fact, approximately 50% of women with hyperprolactinemia have a prolactinoma.[1] These are most often diagnosed in women age 20 to 40 years.[5] A small number of these tumors will secrete both PRL and growth hormone.[1,5,6] Almost all prolactinomas are benign.[1,4] Microadenomas, tumors less than 1 cm, generally produce PRL levels lower than 200 ng/mL. Macroadenomas in the range of 1 to 2 cm produce PRL levels from 200 to 1,000 ng/mL, whereas macroadenomas more than 2 cm can produce PRL levels higher than 1,000 ng/mL.[7] Other pathologic causes of increased PRL include chest wall injuries, cirrhosis, renal failure, polycystic ovary syndrome, and primary hypothyroidism.[1,2,6–9] Any disease process or injury that prevents dopamine delivery to the anterior pituitary gland such as hypothalamic-pituitary stalk injury secondary to surgery or trauma, other pituitary tumors, or diseases that infiltrate the hypothalamus such as sarcoidosis will increase PRL levels.[1,2,10,11]

Drug-induced hyperprolactinemia

Many drugs are known to cause hyperprolactinemia, primarily through the pharmacologic action of reducing hypothalamic production of dopamine or blocking the dopamine binding sites. Most notable are the first-generation antipsychotics (chlorpromazine, fluphenazine, prochlorperazine, haloperidol) and the second-generation antipsychotic (risperidone).[1,2,5,12] Newer antipsychotics (asenapine, iloperidone, lurasidone) may cause elevation of serum PRL but less elevation than the older medications.[13] Metoclopramide, the antihypertensives methyldopa and verapamil, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) increase PRL levels.[1,2,5] Cocaine and morphine (and its analogs) can cause acute and chronic PRL elevation.[5] Although PRL levels are generally normal in women using continuous methadone maintenance, administration of methadone can cause a transient, post-dose rise in PRL levels.[14] The frequent use of cannabinoids (marijuana) has been shown to actually decrease PRL levels from baseline when compared with nonusers.[15]

Clinical manifestations of hyperprolactinemia

Hyperprolactinemia is often undiagnosed until women present with menstrual irregularities or infertility. Increased PRL secretion inhibits release of gonadotropin-releasing hormone (GnRH). When GnRH is low, hypogonadism occurs because of low levels of luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Hyperprolactinemia is present in approximately 10% to 25% of women with oligomenorrhea or amenorrhea, 30% of women with infertility, 30% of women with galactorrhea, and 75% of women with both amenorrhea and galactorrhea.[16,17] Of premenopausal women with prolactinomas, 90% experience



oligomenorrhea or amenorrhea and up to 80% have galactorrhea.[7]

Because of the preexisting hypoestrogenic state, hyperprolactinemia is rarely symptomatic in menopause unless pituitary tumors are causing galactorrhea, headache, or other manifestations of decreased pituitary function.

History and physical exam

Initial evaluation of any menstrual irregularity, amenorrhea, or infertility should begin with a complete menstrual history including age of menarche, frequency, and amount and duration of bleeding. A detailed sexual and pregnancy history should be obtained along with duration of time trying to conceive if relevant. If a woman complains of breast discharge, it is important to ask about current or previous breastfeeding, breast stimulation, breast tenderness, masses, changes in breast texture, skin changes on the breast, or history of chest wall trauma. A detailed medication history is important particularly for SSRIs, antipsychotics, metoclopramide, verapamil, and use of hormonal contraception or other hormonal medication. The review of systems should specifically ask about symptoms of neurologic changes (headache, blurred vision), hypogonadism (vasomotor symptoms, irregular or absent menses, vaginal dryness, mood changes), hypothyroidism (weight gain, fatigue, constipation, cold intolerance, changes in texture of hair and skin), and renal disease. The physical exam should focus on signs of decreased estrogen support (vaginal dryness/atrophy, weight gain, increased hair growth), hypothyroidism (goiter, delayed relaxation with deep tendon reflex testing, hair and skin texture), and visual field disturbances (blurred vision, decreased unilateral/bilateral peripheral vision, difficulty in reading). Patients with elevated PRL levels who are experiencing headaches or visual field disturbances should be referred promptly to a neurologist for further evaluation as these findings may indicate increased intracranial pressure or pressure on the optic chiasm from a macroadenoma.[1,5,7]

Laboratory assessment/imaging

If hyperprolactinemia is suspected, a PRL level should be obtained at the time of initial visit. If the PRL level is normal (< 20 ng/mL), no further testing is required. Because as many as 43% of women with elevated PRL levels also have subclinical hypothyroidism, a thyroid-stimulating hormone (TSH) and free thyroxin (free T4) should also be obtained.[18] Because food, exercise, breast stimulation, and sexual activity can raise PRL levels, a PRL level of 21 to 40 ng/mL should be reevaluated with an early-morning fasting specimen obtained within 1 to 2 hours of awakening for greater accuracy in confirming hyperprolactinemia. For women using methadone for maintenance, the PRL level should be drawn before the daily dose is given.[14] For women taking an antipsychotic medication known to cause hyperprolactinemia, if after consultation with her prescribing mental health provider it is deemed safe to stop the medication, a repeat prolactin level should be obtained 3 days after discontinuation of the medication.[7] Dynamic testing for increased PRL (specimens obtained every 15 minutes for 4–5 samples) is not recommended.[7] PRL level greater than 25 ng/mL in premenopausal women confirms the diagnosis of hyperprolactinemia.[5,7] If a woman presents with breast discharge, galactorrhea can be confirmed with observation of fat globules on microscopic examination of the fluid.

Imaging to assess for pituitary tumors is recommended for any woman with increased PRL regardless of level unless there is known decreased renal function or known use of drugs that cause hyperprolactinemia. Any woman with an increased PRL level who has neurologic symptoms should have prompt imaging to evaluate for a pituitary tumor.[1,5,7] Because of its effectiveness of diagnosis, gadolinium-enhanced magnetic resonance imaging is the preferred method of evaluation.[7] In women with pituitary adenomas, symptoms often correlate with the level of serum PRL. With markedly elevated PRL greater than 100 ng/mL, amenorrhea and symptoms of hypogonadism (hot flashes, vaginal dryness, osteoporosis) occur. Oligomenorrhea or amenorrhea may occur at levels of 50 to 100 ng/mL. At PRL levels of 20 to 50 ng/mL, menses may or may not be affected but infertility

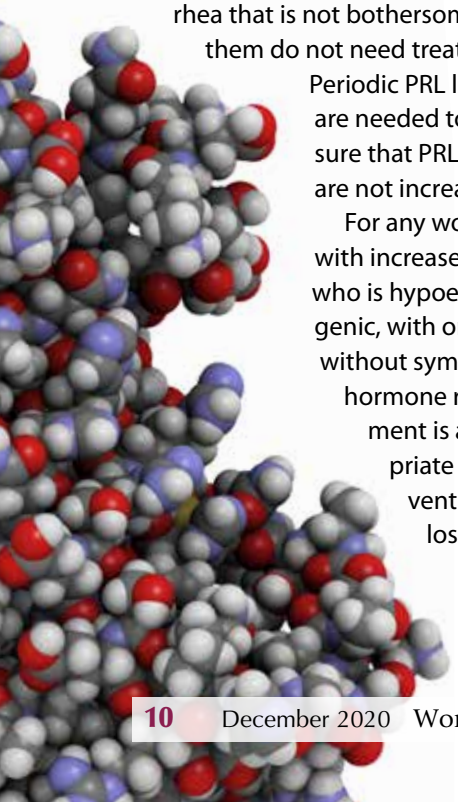
may occur because of inadequate production of progesterone in the luteal phase.[5,7,19]

Treatment and management of hyperprolactinemia

In the reproductive-age woman with hyperprolactinemia, the purpose of treatment is to normalize PRL levels, restore normal ovarian function, and to eliminate galactorrhea. After initiation of treatment, fertility may return before PRL levels normalize and periods return. For women wishing to conceive, it is recommended that they stop their dopamine agonist when the first period is missed with a positive pregnancy test.[7] For women who have drug-induced hyperprolactinemia who wish to conceive, consultation with their mental health prescriber is needed before any change in medication is made.[7]

Premenopausal women with elevated PRL not wishing to conceive and postmenopausal women should be offered reassurance that treatment is not necessary with or without a microadenoma.[7] As well, women who experience galactorrhea that is not bothersome to them do not need treatment. Periodic PRL levels are needed to assure that PRL levels are not increasing.[7]

For any woman with increased PRL who is hypoestrogenic, with or without symptoms, hormone replacement is appropriate to prevent bone loss.[7]



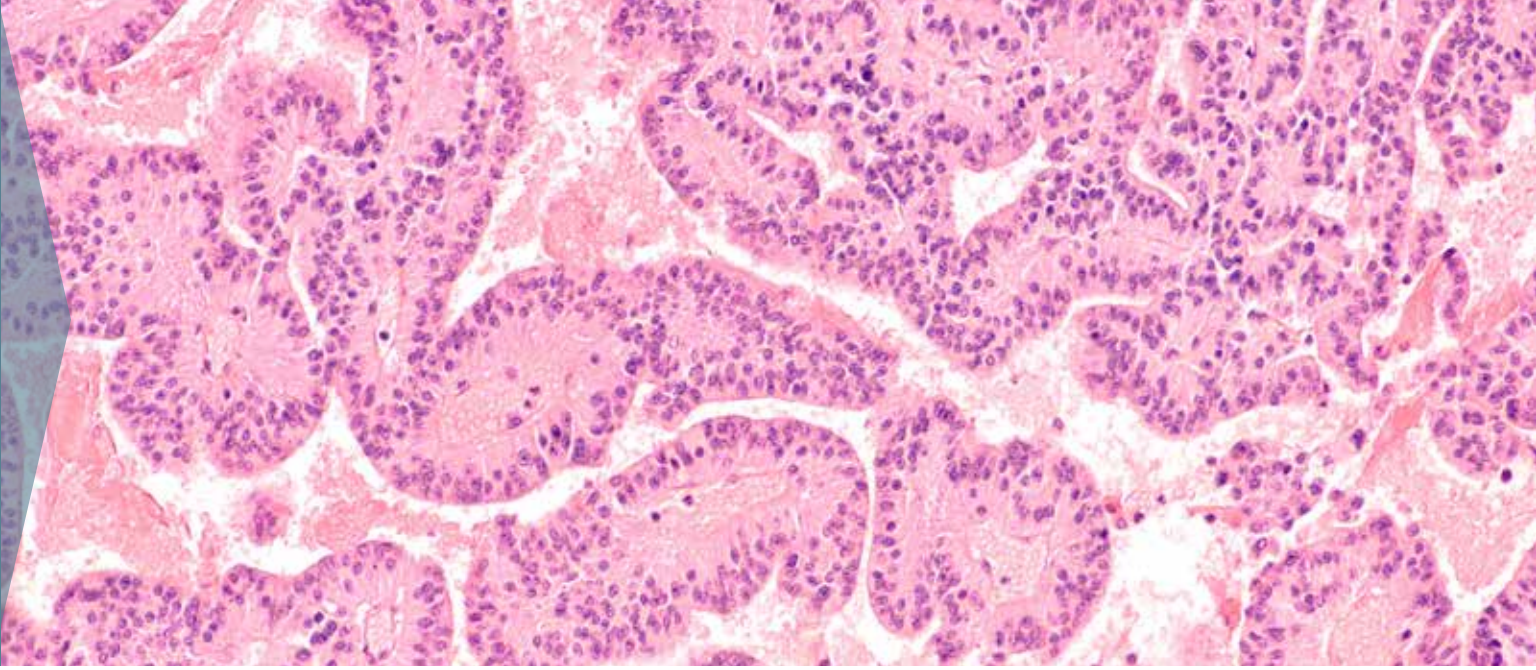
Many of these women will present with infertility, oligomenorrhea, amenorrhea, and/or galactorrhea. Most commonly, a prolactin-secreting tumor in the anterior pituitary gland is the cause.

The following treatment recommendations are based on the guidelines from the Pituitary Society and the Endocrine Society for the diagnosis and management of prolactinomas.[7,20]

Bromocriptine and cabergoline are ergot-derived dopamine agonists that provide effective oral treatment for hyperprolactinemia. Bromocriptine and cabergoline not only decrease PRL levels but also decrease the size of prolactinomas. Biologic response is more important than absolute PRL levels because many women, with treatment, will regain gonadal function and fertility even if PRL levels do not completely normalize.[7]

Cabergoline, because of its greater effectiveness and ease of use, administered once or twice weekly, is preferred over bromocriptine administered daily. When beginning therapy, it is prudent to begin "low and slow." Initiate treatment with cabergoline 0.25 mg twice a week or 0.5 mg once weekly. After 1 month, a PRL level should be obtained to assess effectiveness. If PRL levels remain elevated, the cabergoline dose can be increased every 4 weeks by 0.5 mg once or twice weekly.[7,20,21] PRL levels are obtained monthly until levels normalize. For most women, a total weekly dose of more than 3 mg is rarely needed. Once PRL levels normalize, current therapy is maintained.[7,20] Reports of valvular heart disease are associated with high doses of cabergoline used to treat Parkinson disease. Women should be reassured that with total weekly doses of cabergoline of 2 mg or less as used for the treatment of hyperprolactinemia, the risk of valvular heart disease is not seen.[21,22] If the cost of cabergoline is an issue, bromocriptine 0.625 to 1.25 mg daily can be initiated. Daily dosing should be increased gradually every week until a dose of 2.5 mg once or twice daily is achieved. If the woman experiences postural hypotension or gastrointestinal symptoms, consider dosing at bedtime with food. PRL level monitoring is the same as for cabergoline.[7,20] Side effects of bromocriptine include nausea and vomiting, orthostatic hypotension, nasal congestion, digital vasospasm (Raynaud's), and constipation. These adverse effects are less severe with cabergoline. Side effects can be minimized by initiating treatment with low-dose medication and increasing as needed.

With both cabergoline and



bromocriptine, if after 2 to 3 years of therapy PRL levels are normal, gonadal function has returned, and any prolactinoma is either no longer visible or has been greatly reduced, therapy can be tapered and discontinued.[7,20] Because only 5% to 10% of microadenomas progress to macroadenomas, follow-up imaging is not generally necessary unless the woman demonstrates signs or symptoms of an enlarging tumor.[20]

If a woman is diagnosed with a prolactin-secreting macroadenoma, it is reasonable to immediately initiate treatment with either cabergoline or bromocriptine. However, referral to a provider with expertise treating macroadenomas is needed.

Implications for practice

Nurse practitioners who provide women's healthcare must be able to identify and provide initial assessment of women with possible hyperprolactinemia. Many of these women will present with infertility, oligomenorrhea, amenorrhea, and/or galactorrhea. Most commonly, a prolactin-secreting tumor in the anterior pituitary gland is the cause. First- and second-generation antipsychotic drugs, SSRIs, TCAs, and certain antihypertensive drugs are also known to increase PRL levels.

Once the cause of the hyperprolactinemia is determined, the nurse practitioner should be able to inform women about management options appropriate to their specific needs. If prolactin levels and imaging identify a pituitary tumor, women can be safely treated with either cabergoline or bromocriptine with careful patient monitoring. As PRL levels decrease or normalize, menstrual disorders and galactorrhea will eventually resolve. With the return of gonadal function, fertility also returns. For women with drug-induced hyperprolactinemia, treatment is not necessary in the absence of a pituitary tumor. ●

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