Hyperprolactinemia in Women of Reproductive Age

Etiology, diagnosis, and management

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SUMMARY

Galactorrhea-amenorrhea syndrome and infertility are manifestations of elevated prolactin levels. Numerous functional and tumorous conditions can cause hyperprolactinemia; prolactinoma is the most common tumor. The dopamine agonist agent bromocriptine controls hypersecretion, shrinks prolactinomas, and will restore menstruation and alleviate galactorrhea in most patients.

RÉSUMÉ

L'infertilité et le syndrome galactorrhée-aménorrhée sont des manifestations d'une élévation des taux de prolactine. De nombreuses conditions fonctionnelles et tumorales peuvent provoquer une hyperprolactinémie; le prolactinome en est la cause tumorale la plus fréquente. La bromocriptine, comme agoniste de la dopamine, contrôle l'hypersécrétion, diminue le volume des prolactinomes, rétablit le cycle menstruel et atténue la galactorrhée chez la plupart des patientes.

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THE ISOLATION AND PURIFICATION of human prolactin some 20 years ago was an important accomplishment in clinical endocrinology. The development of radioimmunoassays (RIAs) for prolactin made it feasible for the clinician to use the assay, and the importance of prolactin hypersecretion in reproductive endocrine dysfunction is now well established.[1,2]

Identifying the presence of elevated prolactin levels became clinically significant with the development of prolactin-lowering agents, most notably the ergot derivative bromocriptine. This article reviews the role of hyperprolactinemic states in female reproductive disorders.

Regulating prolactin secretion

Normal levels of prolactin range between 5 and 27 μg/L for women and between 5 and 15 μg/L for men. (Because reference ranges used by laboratories vary, your laboratory may use slightly different reference values.) During pregnancy, levels rise; at term, mean maternal and umbilical cord plasma concentrations reach approximately 200 to 250 μg/L. The increase is a result of estrogen-induced hyperplasia of the lactotropes (the prolactin-secreting cells) in the pituitary gland.[2-4]

Prolactin levels regress to nonpregnant ranges by 3 weeks after delivery in mothers who do not breast-feed. In mothers who breast-feed regularly, this decline can be delayed beyond 6 months or more, with the rate of decline influenced by the frequency and duration of feeds. With prolonged breast-feeding, lactation can be maintained in the presence of lower spikes of suckling-induced prolactin secretion.[2,4,5] The tactile stimulus of suckling is transmitted from the nipple via the intercostal nerves and the spinal cord to the hypothalamus, where a complex neuroendocrine signal triggers a hormone spike from the lactotrope.[4,5]

The hypothalamus has an inhibitory action on prolactin release from the pituitary, mediated by a prolactin-inhibiting factor (PIF). Evidence to date supports the theory that this PIF is dopamine derived from the tuberoinfundibular neurones. Dopamine is present in the pituitary stalk vessels, and receptors for this catecholamine are located on the lactotrope. Infusion of dopamine or administration of dopamine agonists (bromocriptine, levodopa, apomorphine) inhibits prolactin release; dopamine receptor antagonists (phenothiazines, metoclopramide, pimozide) stimulate prolactin release.[4] Prolactin-releasing effects are also demonstrable

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for thyrotropin-releasing hormone, endogenous opiate peptides, vasoactive intestinal peptide, and serotonin,[4] but their significance as prolactin-releasing factors under various physiologic conditions requires further study.

Table 1. **CLINICAL CHARACTERISTICS OF HYPERPROLACTINEMIA**

PHYSIOLOGIC CAUSES
• Sleep
• Pregnancy and lactation
• Breast manipulation
• Stress: anesthesia, exercise, surgical procedure
• Coitus
• Postprandial state
CLINICAL PRESENTATIONS
• Galactorrhea-amenorrhea syndrome
• Amenorrhea without galactorrhea
• Anovulatory bleeding
• Luteal phase deficiency
• Delayed puberty

Hyperprolactinemic states result in hypogonadism through inhibition of gonadotropin secretion and suppression of gonadal steroidogenesis.[2,5,6] The physiologic state of lactational amenorrhea and the pathologic state of the galactorrhea-amenorrhea syndrome are classic hypogonadal states associated with hyperprolactinemia. Anovulation usually results when immunoreactive prolactin concentrations exceed 60 μg/L, but ovulatory cycles can persist in about 5% of hyperprolactinemic women, because the prolactin's biologic action in the circulation differs from its immunologic action.

Prolactin is found in the circulation in various molecular forms, called "small," "big," and "big, big." Small prolactin is the most biologically active.[7,8] Routine RIAs do not differentiate between these forms. Women with elevated prolactin levels but normal menstrual cycles can have high levels of biologically weaker larger varieties.[7]

Prolactin is secreted in an episodic fashion, and large increases can be caused by stress and other physiologic factors.[9,10] Thus more than one prolactin assay is needed to confirm a diagnosis of hyperprolactinemia. Various physiologic and nonpathologic causes of elevations in prolactin (*Table 1*) should be excluded. Ideally, blood samples for prolactin assay should be drawn 2 hours after awakening, and not after a meal. For most patients, the ideal time would thus be midmorning when they have an empty stomach. Prolactin levels can be elevated by the stress of minor surgical procedures, including endometrial biopsy.[10] If both surgery and a prolactin assay are planned, the blood should either be drawn first or drawn several hours later when stress-induced changes have subsided.

Factors other than the release of prolactin can make a single assay of prolactin misleading. For one thing, there is some uncertainty about what range should be considered normal, because distribution of prolactin levels within a population does not seem to follow a normal curve; many normal women have values near or above the upper limit. Moreover, there can be considerable variation in two laboratory readings from the same sample.[9,11] Thus, physicians should not jump to conclusions too readily: minor elevations and isolated inconsistently elevated values may not be of pathologic significance.

Clinical evaluation

The goal of clinical investigation is to determine the cause of hyperprolactinemia. *Table 1* shows the clinical presentations of hyperprolactinemia. *Table 2* shows causes of the imbalance. *Figure 1* is a histogram showing prolactin levels among women with various causes of galactorrhea-amenorrhea syndrome and hyperprolactinemia.

Assessment includes the menstrual history, use of medications, and presence of galactorrhea (a white milky secretion from the nipple). The physician should also look for indications of hypothyroidism, symptoms and signs of hypogonadism (vaginal dryness, dyspareunia with vaginal atrophy), and neurologic symptoms and signs that suggest a space-occupying lesion in the central nervous system.

Galactorrhea alone does not necessarily indicate hyperprolactinemia. Many women with galactorrhea have normal prolactin levels and regular menstrual cycles; these women probably experience increased sensitivity of the breast to normal circulating concentrations of the hormone. This sensitivity occurs most often in women who have breast-fed. Further investigation is not required; however, if galactorrhea is intolerable, the problem usually responds to suppression of the prolactin level with bromocriptine.[11]

Basal hormone determinations should include prolactin and thyrotropin assays. Thyroid hormone, growth hormone, gonadotropins, and estradiol assays can also be helpful. Some patients with hyperprolactinemia exhibit symptoms and signs of androgen excess (hirsutism, polycystic ovary syndrome); assay of dehydroepiandrosterone sulfate and testosterone can be helpful in these women.

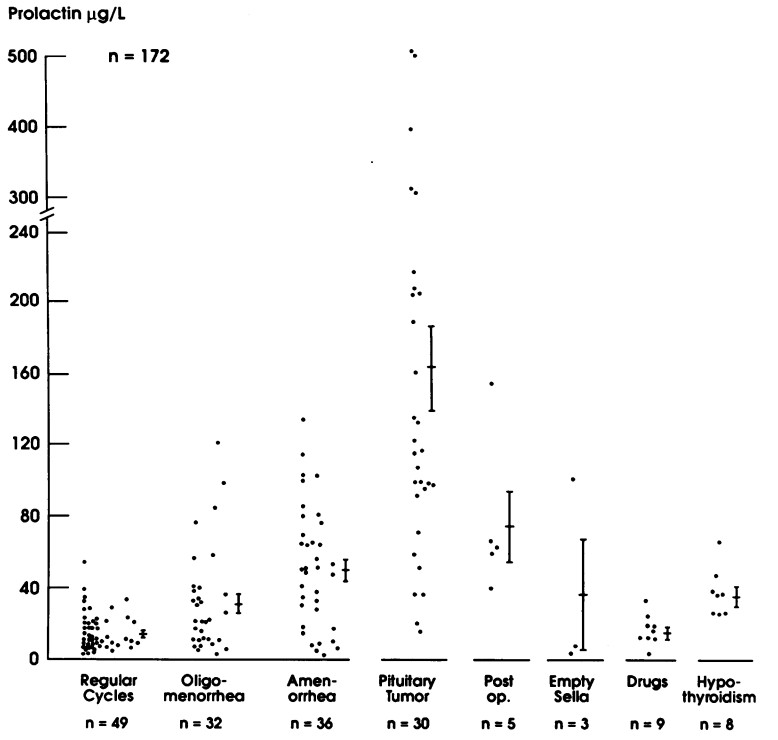
Prolactin should be assayed in amenorrheic women without galactorrhea, if there is no physiologic explanation of the amenorrhea. About 15% of such patients are hyperprolactinemic.[12] Routine skull films of the pituitary fossa will often detect expansion of the sella and calcified mass lesions, such as craniopharyngioma. Where symptoms and signs suggest a central nervous system tumor, computerized axial tomographic (CAT) scanning is indicated.

The prevalence of a prolactinoma is about 60% in women with prolactin levels higher than 100 μg/L, and very high with prolactin levels higher than 250 μg/L.[13,14] Most of these are microadenomas (lesions less than 10 mm in diameter). Macroadenomas are larger tumors, which often show evidence of enlargement of the sella on plain skull films. Because the initial management of microprolactinomas is medical, the same as when no tumor can be detected by radiologic study, it is not essential to prove their presence in all hyperprolactinemic women.[12] When the prolactin level is mildly elevated (less than 100 μg/L) and the clinical findings and skull films of the sella do not suggest a tumor, information from a CAT scan is unlikely to affect management. When prolactin levels are higher, the prevalence of tumors is also increased, and a CAT scan is more likely to detect a

Table 2. **PATHOLOGIC CAUSES OF HYPERPROLACTINEMIA**

CONDITIONS NOT ASSOCIATED WITH PITUITARY TUMOR
Idiopathic (presumed functional cause)
Drug induced • Ovarian steroids • Metoclopramide • Cimetidine • Phenothiazines • Tricyclic antidepressants • Reserpine
Primary hypothyroidism
Hypoadrenalism
Renal failure
Chest wall lesions • Herpes zoster • Burns • Chest wall surgery
Pseudocyesis
CONDITIONS ASSOCIATED WITH PITUITARY FOSSA AND OTHER CNS TUMORS
Prolactinoma
Acromegaly
Empty sella syndrome
Primary hypothyroidism with thyrotropic hyperplasia
Non-secreting pituitary tumor
Craniopharyngioma
Syndrome of multiple endocrine neoplasia
Nelson's syndrome
Cerebral tumors
Secondary metastasis
MISCELLANEOUS CAUSES OF HYPERPROLACTINEMIA
Granulomatous conditions • Tuberculosis • Sarcoidosis • Histiocytosis
Trauma to the pituitary stalk
Ectopic production • Hypernephroma • Bronchogenic carcinoma

Figure 1. **DATA FROM 172 WOMEN WITH GALACTORRHEA-AMENORRHEA SYNDROME AND VARIOUS CAUSES OF HYPERPROLACTINEMIA ARE SHOWN:** *Prolactin levels increase with onset of psychodisruption (oligomenorrhea and amenorrhea) and with high prolactin levels, as seen with tumorous causes of hyperprolactinemia. In women with galactorrhea without cycle disruption, prolactin levels are clustered near normal ranges, with mean values within the normal range (up to 27 μg/L).*



Postop = postoperative (recurrence and incomplete resection). Data shown as mean and standard error.

tumor. In the presence of symptoms and signs indicative of mass neurologic lesion, regardless of the prolactin level, CAT scans or magnetic resonance imaging (MRI) can provide a clearer evaluation of the patient's status.

In the presence of macroprolactinoma with suprasella extension, visual field studies are indicated to determine whether the optic nerve is compressed.

In selected women with a long history of untreated hyperprolactinemia, amenorrhea, and hypoestrogenism with or without other risk factors for osteoporosis, bone density studies may be considered. Apart from the symptoms and local signs of genital atrophy noted earlier, chronically hypoestrogenic women also fail to exhibit withdrawal bleeding in response to a progestin challenge, such as oral medroxyprogesterone acetate, 10 mg daily for 10 days.

Management of hyperprolactinemia

The management may be individualized on the basis of clinical findings, the underlying cause of the elevated prolactin level (if known), the presence of hypogonadism, and the presence of infertility. Several treatment options are available.

Observation only. Women with functional hyperprolactinemia who have no local pelvic signs of hypoestrogenism, who exhibit withdrawal bleeding to progestin challenge, and who are not concerned about infertility may be followed without active intervention. Annual clinical review and prolactin assay may suffice if the clinical condition remains stable. Because these women may spontaneously ovulate from time to time, contraceptive advice should be provided. Surveillance is required

because prolactinomas occasionally develop and hypogonadism commonly occurs, so medical intervention may become indicated.

Elimination of known cause. Elimination of the underlying cause is the ideal treatment, if at all possible. When the problem is drug induced, the physician should consider whether the medication can be discontinued or replaced with another agent not inducing elevation in prolactin.

Treatment of hypothyroidism and hypoadrenalism. In hypothyroid women, thyroid replacement therapy often restores the elevated prolactin level to normal. In women with long-standing primary hypothyroidism and sella enlargement, thyroid replacement therapy usually corrects the associated hyperprolactinemia and reduces the enlarged sella.[14] If the prolactin level does not respond to adequate thyroid replacement, bromocriptine may be required to treat the hyperprolactinemia. In hyperprolactinemia associated with hypoadrenalism, replacement treatment with corticosteroids lowers prolactin levels.[14]

Drug therapy. The mainstay in the pharmacologic treatment of hyperprolactinemia is the use of the dopaminergic agonist bromocriptine. The technique of initiating therapy and maintaining a patient receiving this agent will be described later. Indications for the use of bromocriptine include infertility with anovulation or luteal phase deficiency, symptoms associated with hypogonadism, and symptomatic galactorrhea.

Bromocriptine restores menstruation and ovulation in most women. Contraception is required for women who wish to avoid pregnancy. (The contraceptive options available to hyperprolactinemic women will be reviewed later.) In infertile women, basal temperature recordings are useful to detect the return of ovulation and to document a prolonged luteal phase so that human chorionic gonadotropin assay can be done to confirm pregnancy. Otherwise, pregnancy can go undetected for some time if a previously amenorrheic woman ovulates and conceives before menses are reestablished. It is important to detect pregnancy early; bromocriptine should be discontinued when pregnancy is diagnosed.

In the absence of other infertility factors, hyperprolactinemic women successfully treated with bromocriptine are as fecund as normal women. There is no increase in congenital malformations, multiple pregnancy, or spontaneous abortion.

In hyperprolactinemic women with hypogonadism, treatment with bromocriptine allows resumption of normal ovarian hormone secretion. If the patient cannot tolerate bromocriptine, estrogen-progestin therapy should be considered to alleviate hypogonadism, in particular to prevent symptoms of genital atrophy and the premature onset of osteoporosis.

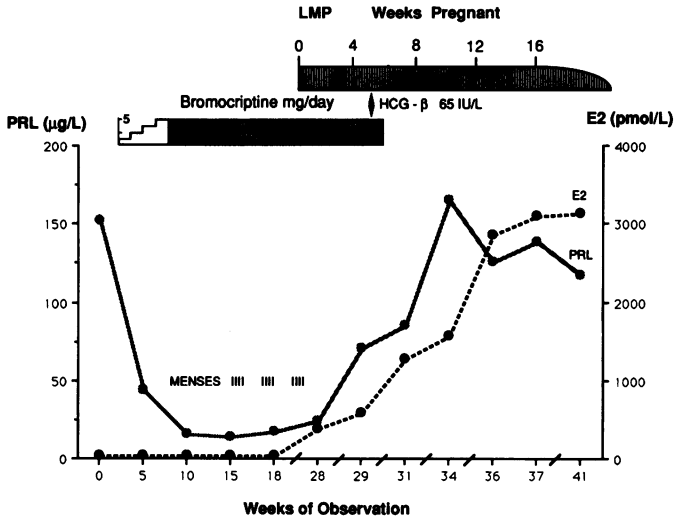
Patients with functional hyperprolactinemia commonly experience relapse when medication is withdrawn.

Because effective doses of bromocriptine vary, and because side effects can be annoying, the drug should be introduced gradually. Common side effects are nausea, vomiting, dizziness (often associated with orthostatic hypotension), headache, and nasal congestion. Alcohol can enhance side effects induced by the drug, so patients should be cautioned accordingly. In the first week, 1.25 mg should be taken in the evening with food. If side effects are not too troublesome (as determined by the patient), a second dose of 1.25 mg with food in the morning is added. Following the same procedure, doses are increased until the patient is taking 2.5 mg morning and night.

Further details on the use of bromocriptine and the endocrine response in a cycle of conception are illustrated by the case of a 32-year-old woman with galactorrhea-amenorrhea syndrome of 5 years' duration *(Figure 2)*. She had a pituitary microadenoma but wished to conceive. When treated with bromocriptine (with doses increased incrementally), cyclic menstruation returned and prolactin levels declined. Once results of tests for human chorionic gonadotropin were positive, bromocriptine was withdrawn. No complications of the tumor developed during pregnancy, and a normal infant was born at term.

When side effects are encountered, the lowest possible dose should be maintained until tolerance is established. The prolactin level is estimated at 3- to 4-week intervals until the circulating level is restored to normal, if possible, with the dose of medication

Figure 2. **COURSE OF BROMOCRIPTINE THERAPY IN WOMAN WITH GALACTORRHEA-AMENORRHEA SYNDROME AND PITUITARY MICROADENOMA:** *Note increase in prolactin levels during early pregnancy and elevation in estradiol at onset of ovulatory menstruation and during early pregnancy.*



Bars on horizontal axis refer to change in the scale. Normal prolactin (PRL) levels before pregnancy up to 27 μg/L, estradiol (E2) levels up to 2202 pmol/L.

titrated according to the prolactin response and the tolerance of the patient. It is uncommon for women with hyperprolactinemia to require more than 5 to 7.5 mg daily in two or three divided doses. If oral medication is not tolerated, intravaginal insertion of the tablets has been shown to be effective while alleviating some troublesome side effects.[15]

Treatment of prolactinoma

Small pituitary adenomas appear to be common entities, being found in 6% to 24% of unselected autopsies.[16] Prolactinomas are the most common pituitary tumor.[14,16] Better diagnostic methods, rather than such other factors as the use of oral contraceptive steroids, have resulted in the increased recognition of prolactinomas.[17]

Because we know little about the natural history of the clinical course of these tumors and there is limited clinical experience with their treatment, it is hard to define the ideal therapeutic approach. Microprolactinomas rarely, if ever, expand; macroprolactinomas are comparatively uncommon.[18]

The goals of treatment are to prevent hormone hypersecretion, to eliminate the tumor if possible or to reduce it or stop it from growing, and to relieve the effects of pressure on adjacent structures. It is beyond the scope of this review to discuss in detail the pros and cons of treatment options. These are discussed elsewhere.[14,18-23] A brief review of medical treatment, surgery, and radiotherapy will be provided.

Dopamine agonist drugs. Medical treatment with dopamine agonists achieves all the goals of treatment. Not only do such agents suppress hormone hypersecretion, but they have also been shown to significantly shrink both small and large prolactinomas.[11-14,18-23] No dopamine agonists other than bromocriptine are currently available for routine clinical use, but newer preparations are being developed. Clinical trials suggest that dopamine agonists not derived from ergot are effective and have fewer side effects than bromocriptine.[24]

Medical treatment offers clear advantages: it is easy to administer, avoids invasive procedures, such as surgery, and does not have the morbidity of radiotherapy. Not all women, however, are tolerant or compliant, and not all respond. Moreover, treatment is long term, usually palliative, and expensive. Bromocriptine can be safely employed in patients with microadenoma and macroadenoma without chiasmal compression. In the

presence of a large tumor and major chiasmal compression, surgical decompression is indicated. With minor chiasmal compression, the decision whether to shrink the tumor with bromocriptine or to use surgery should be made individually.[18,19] In women on long-term treatment, medication should be discontinued periodically to determine whether hyperprolactinemia is in remission. (Suggested intervals range from 1 to 5 years; a trial every 2 years or so seems reasonable.) If it is, particularly if the tumor has shrunk, treatment can be suspended and the patient kept under surveillance. Treatment can be reinstituted if hyperprolactinemia recurs.

Between 64% and 100% of patients with microprolactinomas attain normal serum prolactin levels and show improvement of galactorrhea. Ovulatory menstruation returns in 57% to 100% of women within 6 months.[19] With macroadenomas, prolactin levels do not respond as quickly. But in more than half of treated patients, the tumor is reduced by more than 50% of its original size. In one study, tumors were noticeably smaller within 6 months.[23] Tumors can re-expand, and hyperprolactinemia can recur once bromocriptine is discontinued.

Surgery. Transphenoidal adenectomy performed by experienced surgeons can be followed by reduction of prolactin values to normal in 50% to 90% of cases of small microadenomas. For larger tumors, the success rates fall to as low as 11%.[14] The response to surgery is also influenced by the height of the prolactin elevations. With prolactin levels less than 200 μg/L, the "cure" rate is 74%; when prolactin exceeds 200 μg/L, the cure rate falls to 30%. Within 5 to 10 years after surgery, elevated prolactin levels can recur in up to 50% of patients with microadenomas and 80% of patients with macroadenomas.

Morbidity associated with surgery is rare but includes hemorrhage, leakage of cerebrospinal fluid, meningitis, diabetes insipidus, and hypopituitarism.[14,18-23] The morbidity and mortality of transphenoidal surgery are 0.45% and 0.18%, respectively.[23] Surgery is usually reserved for patients who are intolerant of or unresponsive to drug therapy or who have large tumors and pressure effects, such as severe chiasmal compression. Pituitary apoplexy is a surgical emergency.

Irradiation. Conventional radiotherapy results in a slow fall in prolactin levels; months or years can pass before levels become normal. Following radiotherapy, hypopituitarism may be unavoidable.[14,18-20] Radiotherapy is not a practical way to restore fertility because of the delay in the prolactin response; moreover, the risk of tumor expansion during pregnancy is lower than the long-term risk of developing hypopituitarism as a complication of treatment.[23]

Combined treatment. The effect of bromocriptine in shrinking large tumors can be quite dramatic. Hence, preoperative drug therapy can help to shrink a large tumor before surgery. Drug therapy can also control residual tumor deposits and hyperfunction after surgery or radiotherapy.

Pregnancy and lactation. Estrogens can induce enlargement of prolactinomas. In 5% of women with previously untreated microadenomas, symptoms of tumor expansion (headache, visual field defect, or diabetes insipidus) occurred.[21] Of patients with previously untreated macroadenoma, 36% developed tumor-related complications. Such complications occurred in only 7% of patients who had been treated before conception.[21] In a more recent review,[23] only 1.6% of women with microadenomas had symptoms of tumor enlargement (headaches, visual disturbances, or both), while 4.5% had asymptomatic tumor enlargement revealed by radiologic study. In pregnant women harboring untreated macroadenomas, 15.5% had symptomatic tumor enlargement, while 8.9% experienced asymptomatic tumor enlargement. In women with macroadenomas who conceived after receiving treatment (surgery or radiotherapy), only 4.3% experienced symptomatic tumor enlargement and none had asymptomatic enlargement during gestation.[23]

Patients with a microadenoma and selected patients with macroadenoma contemplating pregnancy can therefore be managed conservatively. In the patient with macroadenoma, treatment with bromocriptine for 6 to 12 months before conception is contemplated can shrink the tumor.

Monthly clinical review can be used to assess whether symptoms and signs of tumor enlargement are occurring. Headache, progressive visual field loss (slight bitempo-

ral hemianopsia may be normal during pregnancy), symptoms of hypopituitarism, and diabetes insipidus require more detailed evaluation. Serial prolactin assays during pregnancy are not helpful in predicting tumor expansion during gestation.[23]

When tumor enlargement is detected (increasing visual field loss and changes on CAT or MRI scan), delivery may be considered if the fetus is mature. When delivery is not feasible, the treatment of choice is to reinstitute bromocriptine. This is effective in preventing further tumor expansion and reducing the tumor size.[14,18-23] Indications for surgery during pregnancy are severe chiasmal compression by a tumor unresponsive to drug therapy and the rare occurrence of pituitary apoplexy. Whenever possible, defer the operation until after delivery.

Breast-feeding does not pose any demonstrable risk to the mother with a prolactinoma.[15] When there is a need to suppress lactation, bromocriptine is the drug of choice.

The status of the tumor should be assessed 3 months after weaning. When indicated, further treatment with bromocriptine could be initiated.

Contraception. Because estrogens can stimulate lactotrope hyperplasia and hypertrophy, the long-term safety of oral contraceptives in women with prolactinomas requires elucidation. Prolactinomas are not necessarily a contraindication for the oral contraceptive pill, but, if acceptable, other methods of contraception would be a better choice to avoid any concern about potential adverse effects of long-term exposure to sex steroids. If oral contraceptives are used, low-dose preparations are preferred. The patient should be taking bromocriptine, and her tumor should be kept under observation. Parous women without atrophy of the uterus due to hypogonadism induced by elevated prolactin levels can use the intrauterine device if there are no clinical contraindications.

Conclusion

Galactorrhea-amenorrhea syndrome and infertility are well-recognized manifestations of elevated prolactin levels in women of reproductive age. Hypogonadism resulting from hyperprolactinemia can be associated with local genital atrophy and, when long lasting, increases the risk of osteoporosis. However, not all hyperprolactinemic women are hypoestrogenic. Physiologic and numerous nonpathologic factors can result in elevated prolactin levels. These factors must be taken into account before a diagnosis of hyperprolactinemia is made. Pathologic causes of hyperprolactinemia include other endocrinopathies and tumors in the region of the hypothalamic pituitary axis.

The prolactinoma is the most common tumor of the pituitary gland and is usually identified in the presence of the galactorrhea-amenorrhea syndrome with very high prolactin levels. Amenorrhea without accompanying galactorrhea occurs frequently enough that prolactin assays are warranted when amenorrhea occurs without a physiologic or other nonpathologic cause. The dopamine agonist bromocriptine is effective in controlling prolactin hypersecretion and in reducing prolactinomas. In women tolerant of bromocriptine, prolactin hypersecretion is effectively controlled with resumption of ovulatory menstrual cycles and alleviation of symptomatic galactorrhea in most instances. ■

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