Hyperprolactinemia and Menstrual Dysfunction

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The application of prolactin measurement in the evaluation of anovulatory states in the presence or absence of galactorrhea has revealed that abnormal prolactin secretion is frequently associated with amenorrhea and other menstrual dysfunctions. Despite this recognized clinical association, the precise mechanism involved in the pathogenesis of hyperprolactinemic anovulation is not well understood. Current evidence suggests that disordered catecholamine metabolism within the hypothalamus has a pivotal role in the disruption of normal ovulatory function. After reduction of elevated prolactin to normal levels by surgical removal of a lactotropic adenoma or by administration of a dopamine agonist, restoration of cyclic menses may be achieved.

Neuroregulation of Prolactin

Control of prolactin secretion is unlike that of other anterior pituitary hormones in that it is regulated primarily by a tonic hypothalamic inhibitory factor. The precise nature of this prolactin inhibitory factor (PIF) has not been determined, although a large body of evidence strongly suggests that dopamine is a PIF. In vitro studies have shown that prolactin release from incubated pituitary tissue is inhibited by catecholamines, including dopamine. Similarly, an injection of dopamine into the third ventricle of rats results in a lowering of serum prolactin. These findings are consistent with histochemical immunofluorescent studies that demonstrate the presence of dopaminergic secretory granules adjacent to portal vessels leading to the pituitary gland. In addition, binding studies indicate that dopamine receptors are contained within the anterior pituitary. In man the intravenous infusion of dopamine, or administration of its precursor, L-dopa, promptly suppresses circulating levels of prolactin. Conversely, the administration of metoclopramide or sulpiride, both potent dopamine antagonists, stimulates prolactin release.

The dopaminergic regulation of prolactin release appears to be influenced by a short-loop feedback mechanism. Within the hypothalamus, dopamine-containing tuberoinfundibular neurons secrete dopamine into the portal circulation to effect inhibitory control of prolactin release. Dopamine turnover in these neurons is directly related to circulating levels of prolactin. Furthermore, drugs that block dopamine receptors, thereby causing an increase of prolactin, stimulate dopamine turnover only if the pituitary is intact. In hypophysectomized animals, this capacity of dopa-
mine-receptor-blocking agents is lost, probably due to the absence of prolactin.

The question of whether a physiologic prolactin-releasing factor exists in man remains unanswered. Prolactin-releasing activity has been demonstrated in a variety of animal species but not in man. Administration of thyrotropin-releasing hormone (TRH) in pharmacologic amounts promptly stimulates prolactin secretion in man. Accordingly, in primary hypothyroidism elevated prolactin levels probably result from a compensatory rise of endogenous TRH. However, efforts to establish TRH as a physiologic prolactin-releasing factor have not been successful. Serotonin has been implicated in the release of prolactin. After intraventricular injection of serotonin in rats and intravenous administration of serotonin precursors in man, increases of serum prolactin were found in each group. Episodic rises of prolactin have been correlated with non-REM sleep, which appears to be a serotonin-mediated function. Histamine also may play a role in the regulation of prolactin release. The effect of histamine may be inhibitory, as mediated by its H2 receptor, or stimulatory, involving the H1 receptor.

**Physiologic Prolactin Secretion**

In prepubertal children, circulating levels of prolactin range from 2 to 12 ng/ml. With the onset of puberty, prolactin levels are not significantly altered in boys; whereas a gradual increase is observed in girls, which persists until adult prolactin concentrations are achieved. This increase in serum prolactin is correlated closely with menarche and therefore is attributed to ovarian production of estrogen. In normal adult women the range of serum prolactin concentrations is 5-50 ng/ml. The pattern of its secretion is episodic, rather than regular or rhythmic. Increases in prolactin occur with either daytime or nocturnal sleep. Prolactin levels remain elevated throughout the sleep period and return to presleep values approximately 2 hours after awakening. Recently, it has been shown that the ingestion of food induces a significant rise of prolactin, compared with sham feeding during the same interval. While the underlying mechanism is unclear, it appears that feeding augments prolactin secretion. During the menstrual cycle, mean prolactin concentrations do not vary markedly, although subtle increases have been noted at midcycle and in the luteal phase. These findings are consistent with the greater prolactin response to TRH in normal women at midcycle, compared with that observed in the early follicular phase, and probably reflect the modulative influence of circulating estrogen on pituitary lactotropes. Daily prolactin levels may vary considerably and occasionally exceed the established upper normal range of values. Consideration of this day-to-day variation of prolactin release clearly has an impact on the significance of mild hyperprolactinemia determined from a single prolactin measurement. Other physiologic factors that may induce a rise of prolactin are exercise, stress, coitus, and nipple stimulation.

In pregnancy, maternal prolactin levels increase steadily from the 7th week of gestation to achieve concentrations 20 times basal levels at term. This rise is probably due in large part to the increase in circulating maternal estrogens, which in early pregnancy precedes the initial increment of prolactin by several days. Following pregnancy, basal prolactin levels return to normal within 4 weeks in non-breast-feeding mothers. In nursing mothers, the decline of serum prolactin to nonpregnant concentrations is less rapid and usually occurs within 80-100 days, although it has been reported that elevated levels may persist beyond this interval. With suckling, increases in serum prolactin are observed, the magnitude of which is dependent upon the basal concentration and the degree of nipple stimulation. Peak prolactin levels occur at about 30 minutes after the onset of suckling and return to basal levels within 3 hours following the discontinuation of the stimulus. As a
woman experiences declining reproductive function associated with aging, serum prolactin levels decrease. This change is correlated with the reduced levels of circulating estrogen observed in perimenopausal as well as postmenopausal women.

**Biologic Action of Prolactin**

In man the only recognized function of prolactin is the promotion of lactogenesis during pregnancy. The process of lactogenesis appears also to involve estrogen, progesterone, cortisol, insulin, and human placental lactogen. Estrogen and progesterone serve to stimulate alveolar and ductal development in the breast, respectively; whereas prolactin, cortisol, and insulin are required for the induction of a specific messenger ribonucleic acid (mRNA) for casein synthesis. Prolactin is also instrumental in the biosynthesis and release of lactalbumin, milk fat, and lactose.

Paradoxically, whereas estrogen and progesterone have this stimulatory effect on the breast in pregnancy, these steroids, particularly progesterone, also inhibit lactation and interfere with lactogenesis. In animals, prolactin induction of its own receptor in mammary tissue is blocked by progesterone. Progesterone also inhibits mRNA synthesis of casein in a dose-dependent manner. Whereas the identification of prolactin receptors in mammary tissue corresponds with the necessary lactogenic function of prolactin, the finding of prolactin receptors in other tissues has not been associated with a complementary physiologic role for prolactin. Prolactin receptors have been found in the ovary, and measurable amounts of prolactin are contained within human follicular fluid, but the significance of these findings remains unclear. The presence of prolactin binding in the adrenal gland suggests an effect of prolactin, although neither a physiologic nor a pathologic relationship has been established. Cultured granulosa cells exposed to excess prolactin antiserum or grown in a culture medium devoid of prolactin produce and secrete less progesterone than control levels. These findings support earlier data, which suggests that prolactin is important for steroidogenesis due to its ability to influence the amount of cholesterol available for metabolism to progesterone.

**Causes of Hyperprolactinemia**

**Disorders of Inhibitory Control**

Hyperprolactinemia due to loss of inhibitory control usually involves hypothalamic disease or infundibular compression. Destructive hypothalamic lesions include primary tumors (craniopharyngioma) or metastatic tumors, infiltrative diseases (sarcoidosis, histiocytosis, hemachromatosis), infarction, Parkinson's disease, or surgical or radiation ablation. These disorders probably disrupt dopamine synthesis or activity within the hypothalamus and thus result in loss of the inhibitory control of prolactin. Chronic hypothalamic disease may not always be associated with hyperprolactinemia, suggesting that tropic stimulation from the hypothalamus is necessary for the lactotrope. This is particularly true of the other anterior pituitary hormones. Thus, when the insult to the hypothalamus is severe, prolactin levels may not be elevated and basal concentrations of the remaining anterior pituitary hormones will be depressed.

Compression of the infundibulum or pituitary stalk may be associated with hypothalamic or pituitary tumors, aneurysms, pituitary cysts, the empty sella syndrome, and pseudotumor cerebi. In these disorders the transport of dopamine within portal vessels is interrupted and hyperprolactinemia occurs. Diseases of the hypothalamus and infundibulum are not common. In the absence of a prolactin-producing tumor, loss of inhibitory control of prolactin results in mild hyperprolactinemia. Prolactin levels in excess of 100 ng/ml are seldom encountered.
HYPERPROLACTINEMIA

Pituitary Tumors

Pituitary tumors represent approximately 10% of all intracranial neoplasms. Most of these tumors are hormonally active and originate within the anterior pituitary. The most common lesion is a prolactin-secreting or lactotropin adenoma. Hyperprolactinemia has been shown to occur with most chromophobe adenomas. In the past, these tumors were thought to be nonfunctional. Occasionally a lactotrope adenoma may be found to coexist with tumor cells that produce growth hormone or adrenocorticotropic, giving rise to a mixed-hormone-secreting neoplasm. One should take a careful history and perform a physical examination to exclude Cushing’s disease or acromegaly in adults and gigantism in children. In vitro studies of lactotrope tumor cells have confirmed the immunohistochemical findings consistent with active prolactin secretion. These results substantiate the hypothesis that hyperprolactinemia is due to direct secretion by the tumor itself. Thus, a large lactotrope adenoma could give rise to hyperprolactinemia, directly, from secretion by tumor cells and, indirectly, by compression of portal venous flow and interruption of PIF.

Whether or not pituitary adenomas function autonomously in their production of prolactin remains unclear. It appears that in most patients there is some degree of prolactin responsiveness to provocative stimulation, though not always of the same magnitude as that observed in normal individuals. It is for this reason that the predictive value of prolactin stimulation by TRH and prolactin suppression by L-dopa has not been established. Although a lack of hormone response to stimulation is consistent with a large lactotrope adenoma, these perturbation tests have not distinguished between patients with and without small pituitary tumors. Recently, it has been reported that lactotrope hyperplasia may coexist with a frank lactotrope adenoma. We thus have an explanation for the variable prolactin response to selected stimuli in patients with tumors.\(^3\)

The natural progression of prolactin-secreting pituitary tumors has not been established. Evidence from autopsy studies indicates that pituitary tumors have been found in 3–22% of patients examined.\(^4\) The distribution of these lesions ranges over the entire life span, with a peak incidence occurring in the 6th decade of life. Many of the patients studied were clinically asymptomatic. These findings tend to suggest that pituitary tumors grow slowly. Nevertheless, one must exercise extreme caution in the management of these patients in order to avoid the consequences of rapid tumor enlargement.

Endocrine-Related Disorders

A variety of primary and secondary endocrine disorders may be responsible for hyperprolactinemia, including primary hypothyroidism, diseases resulting in increased estrogen secretion, Nelson’s syndrome and ectopic prolactinoma production. In primary hypothyroidism, serum thyrotropin-stimulating hormone (TSH) levels are usually elevated, probably as a result of increased hypothalamic TRH release. Since prolactin is responsive to the administration of TRH, it is likely that the hyperprolactinemia observed in this disease is due to increased TRH secretion.\(^5\) Whether or not hyperprolactinemia contributes to amenorrhea associated with primary hypothyroidism has not been concluded. In these patients, resolution of all symptoms, including hyperprolactinemia, occurs following administration of replacement thyroid hormone.

Disorders involving excess estrogen secretion may be associated with hyperprolactinemia. Usually the elevation of prolactin is mild to moderate and probably does not represent the major reason for menstrual abnormalities. Significant increases in prolactin may occur with ovarian or adrenal tumors, whereas in polycystic ovarian disease up to 25% of patients are hyperprolactinemic. In patients with cirrhosis of the liver, increased estrogen production results
from increased peripheral conversion of androgen. The capacity of estrogens to induce hyperprolactinemia is mediated in large part by their effect on the lactotrope. It has been demonstrated that estrogen directly promotes pituitary synthesis of prolactin as well as the depleting PIF activity in the hypothalamus.

Other rare conditions in which hyperprolactinemia is found are Nelson’s syndrome and ectopic prolactin production by malignant tumors. In both diseases the prolactin levels may be markedly increased.

**Drug-Induced Hyperprolactinemia**

The number of drugs associated with hyperprolactinemia has grown quite large over the years. The most common encountered medications include sex steroids, antidepressants and tranquilizers, antihypertensives, and certain antihistamines. Exogenous estrogens are capable of stimulating prolactin in both premenopausal and postmenopausal women, although the latter appear to be more sensitive in this regard. Most women using combined estrogen-progesterone oral contraceptives do not develop hyperprolactinemia, although mean circulating prolactin levels may be increased, compared with baseline concentrations. Recently, it has been reported that 30% of the women taking oral contraceptives exhibit elevated prolactin levels. Psychotropic agents (phenothiazines, butyrophenones, tricyclic amines) increase serum prolactin by alteration of dopamine metabolism in the hypothalamus. The probable mechanism of action of these drugs is to block dopamine receptor sites. The presence of dopamine receptors in the pituitary suggests an associated, direct effect on the lactotrope. In comparison, certain antihypertensive medications act as false neurotransmitters (alpha-methyldopa) and deplete PIF stores, whereas others (reserpine, guanethidine) prevent the reuptake and storage of dopamine in the hypothalamus. Cimetidine, a histamine-blocking agent prescribed for peptic disease, may be associated with hyperprolactinemia. Since H2 receptors mediate an inhibitory influence on prolactin release, administration of this drug stimulates a rise of circulating prolactin. Invariably, the degree of hyperprolactinemia observed in patients receiving pharmacologic drugs is mild. Serum prolactin levels are usually in the range of 50 ng/ml, and concentrations above 100 ng/ml are exceedingly rare. In the presence of persistent marked hyperprolactinemia, consideration must be given to underlying disease.

**Nonendocrine Conditions**

Injury to the chest wall or lesions of the breast may increase prolactin concentrations by stimulation of afferent neurogenic pathways. The precise mechanism of this peripheral neurostimulatory reflex is not known, although evidence suggests an alteration in hypothalamic dopamine activity. Chronic renal failure has been associated with mild hyperprolactinemia. Since circulating prolactin levels are correlated with renal function in patients with this disorder, it seems reasonable that the hyperprolactinemia reflects decreased clearance of the hormone relative to impaired glomerular filtration rate.

**Clinical Manifestations**

The presence of galactorrhea with or without amenorrhea suggests the possibility of hyperprolactinemia. In patients with normal ovulatory function, galactorrhea has been poorly correlated with hyperprolactinemia. A prior history of lactotrope stimulation may be elicited from these individuals. Lactotrope stimulation may occur as a result of pregnancy, stress, breast or chest-wall stimulation, or through the use of estrogen-dominant oral contraceptives or psychotropic drugs. An increase of prolactin sufficient to induce galactorrhea apparently may occur, and galactorrhea may persist even when the stimulus for prolactin secretion has ceased. If the galactorrhea is accompanied by amenorrhea, the incidence of hyperpro-
lactinemia is more frequent than in patients with either galactorrhea or amenorrhea only. Most series have reported a 50% or greater association. Some patients with amenorrhea or oligomenorrhea but no demonstrable galactorrhea may also be suffering from hyperprolactinemia. Approximately 20% of amenorrheic patients have been found to have hyperprolactinemia. A similar incidence has been reported in a study of anovulatory oligomenorrheic women, although the mean prolactin level in this group was significantly lower, compared with that of amenorrheic patients. The clinical significance of hyperprolactinemic amenorrhea is accentuated by the recent reports of prolactin-secreting pituitary adenomas in these patients.

Hyperprolactinemia also may be associated with menstrual irregularities stemming from defective corpus luteum function. This disorder is commonly manifested by regular cycles, with a shortened luteal phase or irregular cyclic bleeding. An inadequate luteal phase often may precede the onset of amenorrhea. The diagnosis is suggested by an abnormally short basal temperature elevation in the luteal phase accompanied by deficient progesterone production.

In the presence of hyperprolactinemia the incidence of galactorrhea is approximately 30–40%, although an incidence of 80% was reported in one study. This disparity was attributed to the select nature of the patient population and to very careful breast examination in the latter study. In patients with hyperprolactinemia unaccompanied by galactorrhea, either the circulating concentration of prolactin may be insufficient for adequate breast milk production or the factors which prime the breast for the action of prolactin are not adequate.

**Mechanism of Anovulation**

In hyperprolactinemic amenorrhea several lines of evidence suggest that a central disturbance is most likely responsible, although altered ovarian function cannot be discounted. Measurement of circulating hormones indicates that serum estradiol levels are usually low. In some instances, normal values have been reported that are comparable to those found in the follicular phase of the menstrual cycle. Individual basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations often are normal, but may be decreased. Careful examination of gonadotropin secretion has revealed that the episodic pattern of release is markedly attenuated. Since episodic secretion is mediated by gonadotropin-releasing hormone (GnRH), the lack of LH and FSH pulses indicate impaired hypothalamic GnRH release. In spite of this, substantial increases of LH and FSH have been observed in response to the administration of GnRH. In particular, the increase of FSH after GnRH administration, was shown to be greater than levels of FSH observed in normal ovulatory women studied in the early follicular phase. The heightened FSH response was attributed to decreased estradiol levels in these patients, with consequent loss of the preferential inhibition of FSH by estrogen. Since GnRH is in large part responsible for synthesis and storage of gonadotropins, as well as activation to their releasable form, these results imply that in hyperprolactinemic amenorrhea, altered endogenous GnRH secretion gives rise to an impaired pattern of spontaneous LH and FSH release without affecting gonadotropin production.

The precise role of hyperprolactinemia in the genesis of anovulation has not been firmly established. Studies in animals have suggested that prolactin exerts a feedback effect on hypothalamic dopamine. Induction of hyperprolactinemia in the rat, either by an injection of prolactin or following transplantation of prolactin tissue under the renal capsule, is associated with increased dopamine turnover. In these animals pituitary LH content was decreased. In normal cycling rats, diminished dopamine turnover occurs during the afternoon of proestrus, at which time the LH surge is observed. Fur-
thermore, it has been shown that the intraventricular administration of dopamine blocks the norepinephrine-induced LH surge in estrogen-treated rabbits. Recently, it has been reported that dopaminergic neurons inhibit the release of luteinizing-hormone-releasing factor. These findings, and the fact that dopamine and GnRH neurons are anatomically in close proximity to each other within the hypothalamus lead to the hypothesis that dopamine inhibits GnRH secretion.

There is evidence that, in women, the administration of dopamine to normal and hyperprolactinemic subjects acutely reduces circulating LH levels. However, in one study, the administration of a dopamine agonist, bromocriptine, to hyperprolactinemic women failed to significantly lower serum LH. In that study it was postulated that endogenous dopamine activity was increased in the presence of hyperprolactinemia and caused inhibition of basal LH concentrations and pulsatility. That LH levels were not further suppressed by bromocriptine suggested a maximal inhibitory effect of dopamine on LH in these patients. The concept that LH is inhibited by increased dopamine is supported by the finding that administration of a dopamine antagonist, metoclopramide, induced a rise of LH in hyperprolactinemic patients but not in normal individuals.

Apart from the effects of hyperprolactinemia on gonadotropin secretion, there is evidence suggesting that prolactin may exert a direct effect on ovarian steroid production. In vitro production of progesterone by human ovarian granulosa cells, in the presence of LH and FSH, was inhibited by large amounts of prolactin added to the culture medium. This inhibition of progesterone by prolactin was unaltered by increasing the concentration of LH and FSH. In normal ovulatory women, the induction of hyperprolactinemia by the administration of sulpiride resulted in loss of the luteal phase rise of progesterone and subsequently amenorrhea. These findings are consistent with the observation that women with mild hyperprolactinemia may present clinically with luteal phase defects, marked by regular menstrual cycles, which may or may not be shortened, and infertility. Use of a dopamine agonist to treat these patients usually restores normal luteal function and adequate ovulatory menses.

**Evaluation of Hyperprolactinemia**

In the evaluation of suspected abnormal prolactin metabolism, adequate screening tests include careful history-taking, physical examination, measurement of serum prolactin, and assessment of thyroid function (free thyroxine index or serum TSH). Clearly, evidence of hypothyroidism would warrant appropriate therapy.

The presence of hyperprolactinemia in the absence of any discernible cause indicates the need for evaluation of the sella turcica. This may be accomplished by the use of plain cone-down views, thin-section polytomography, or computerized axial tomography (CT scan). Plain cone-down views will detect neoplasms that grossly distort the normal configuration of the sella. The radiation exposure is low and procedural cost minimal. Thin-section polytomography is more sensitive than cone-down views. With this procedure one is able to detect subtle changes in the sella turcica, which may reflect a pituitary tumor. However, polytomography is associated with increased radiation exposure and cost. In addition, there is a significant incidence of subtle abnormalities in normal individuals undergoing thin-section sellar polytomography that occasionally make the interpretation of results problematic. The most recently developed CT scanners provide a distinct advantage over previous methods in the evaluation of the sella turcica. The configuration of the pituitary gland is actually visualized, and small lesions in the range of 2–3 mm in diameter may be detected. There is also low radiation exposure. However, the procedure is costly. Each method has advantages and
disadvantages of which the clinician should be aware. Obviously, the index of suspicion of a pituitary tumor will dictate the procedure of choice.

If the sella turcica is abnormal, then subsequent appropriate procedures, including testing for visual fields, should be performed to establish a diagnosis. If the sella turcica is normal, then periodic evaluation of the serum prolactin level, visual fields, or sella turcica is important.

A normal serum prolactin level during the initial screening tests usually does not require further sellar evaluation unless the patient is hypoestrogenic. Markedly diminished estrogen levels may be indicative of a large pituitary lesion.

Surgical Treatment of Hyperprolactinemia

Management of hyperprolactinemia disorders consists of surgery, radiation, or medical therapy, depending on the diagnosis. Treatment is directed toward 1) eradication of progressive pituitary tumor enlargement, which may be destructive to adjacent tissue and structures, and 2) restoration of ovulation and cessation of lactation. Large pituitary tumors, or macroadenomas, are greater than 1 cm in diameter and are usually associated with extrasellar extension. These lesions should be treated by either definitive surgery or radiation, or both. Frequently a transfrontal craniotomy is necessary, although some mild suprasellar lesions may be adequately removed by the transsphenoidal approach. Clinical outcome will largely depend on the extent of the disease, the completeness of tumor resection, and postoperative endocrine evaluation. Recently it has been shown that chronic administration of a dopamine agonist, bromocriptine, to patients with large prolactin-secreting pituitary adenomas resulted in a significant reduction in the size of the lesion (Fig. 1). Thus, dopamine agonists may be of great importance as potential adjunctive therapeutic agents in the surgical management of macroadenomas. On the other hand, some pituitary tumors that appear to be prolactin-secreting may not respond to dopamine agonist treatment. The clinical experience in this area is not great, and further investigation is required.

Intrasellar lesions or microadenomas may be treated surgically or medically. Radiation therapy is seldom used as an initial form of treatment. Selective removal of a microadenoma through the transsphenoidal route has been associated with a high degree of success. The advantages of this procedure over that of craniotomy are manifested by a lower incidence of both major and minor complications. The completeness of the resection often is suggested by normalization of prolactin levels. In about 70% of patients, restoration of normal endocrine function usually occurs within 5 months after surgery, with an almost immediate cessation of lactation preceding the return of ovulatory function. Currently long-term follow-up of these patients is being conducted to establish the efficacy of treatment. The most common complication of transsphenoidal surgery is transient diabetes insipidus, although more serious morbidity has been documented, such as postoperative bleeding, cerebrospinal fluid rhinorrhea, and meningitis.

If the patient desires pregnancy, serious consideration must be given to surgical resection of a prolactin-secreting pituitary adenoma. During pregnancy, the normal pituitary gland may enlarge up to twice its size due to the influence of high, circulating estrogen concentrations. As a result, normal ovulating women, without evidence of hyperprolactinemia, occasionally may experience a physiologic visual-field defect. This problem usually occurs late in pregnancy and resolves itself following delivery without residual symptoms. The management of pregnant patients with prolactin-secreting pituitary tumors involves careful history-taking, physical examination, and assessment of visual fields at monthly intervals, whether or not the lesion has been treated.
FIG. 1. CT scan of the sella turcica in a patient with a lactotrophic macroadenoma before treatment (A). A marked reduction in tumor size is evident by 6 weeks (B) and after 6 months (C) of bromocriptine therapy.

Medical Treatment of Hyperprolactinemia

The emergence of dopamine agonists—in particular, bromocriptine—in the treatment of galactorrhea-amenorrhea syndromes has provided a conservative nonsurgical approach to the management of this problem. The limits of their therapeutic usefulness have not yet been established, and relevant studies are currently being performed.

Bromocriptine inhibits prolactin secretion by reducing the mechanism of actual release, e.g., exocytosis, rather than by producing an immediate effect on hormone synthesis. The disruption in prolactin release is initially accompanied by an increase in pituitary prolactin content. Continual administration of bromocriptine eventually suppresses pituitary prolactin content and concentration while maintaining reduced secretion. In addition, there is decreased deoxyribonucleic acid synthesis and reduced mitotic activity. Thus, an alteration in the cellular metabolism of prolactin production appears to occur with prolonged treatment. The action of bromocriptine can be opposed in a dose-dependent fashion by a dopamine antagonist, such as the receptor blocker chlorpromazine. As hormone secretion from prolactin cells is under inhibitory dopamine control, these findings indicate that bromocriptine inhibits prolactin release by stimulating dopamine receptors. The precise interaction of dopamine receptor and hormone release is not known, although it has been postulated that bromocriptine attenuates prolactin release by altering intra-
FIG. 2. Serum LH and FSH concentrations before and during bromocriptine treatment in four patients with hyperprolactinemic amenorrhea. Serum progesterone (P0) levels obtained within 1 week of a typical midcycle LH rise indicate ovulation in each patient. Menses are represented by the horizontal solid bar.

...cellular-free calcium or by interfering with membrane function.

The administration of bromocriptine to patients with galactorrhea or amenorrhea, or both, results in marked improvements of symptoms. With galactorrhea, approximately 80% of these patients will note total cessation or marked reduction in their lactation. Within 1–2 weeks of the onset of therapy, galactorrhea will decrease noticeably; and in the vast majority of patients it will be totally absent by 2 months. For patients with resistant symptoms, prolonged administration of a slightly increased dose of bromocriptine usually results in total abatement of symptoms. Similar findings have been described for those individuals with hyperprolactinemic amenorrhea. In response to bromocriptine, 80% of these individuals will show evidence of ovulation and resume regular cyclic menstrual function (Fig. 2). The onset of this effect is rapid, and initial vaginal bleeding occurs 6–8 weeks from the onset of the use of the drug. By 3–6 months, the incidence of ovulatory menses is about 80%.

The action of bromocriptine on prolactin secretion in hyperprolactinemic women is rapid. Following administration of bromocriptine, there is an acute fall of serum prolactin that is demonstrable within 1 hour and maximal at approximately 8 hours after ingestion. Hence, bromocriptine, in its current form, is administered as a 2.5-mg tablet two or three times a day. Higher dosages may be necessary to reduce prolactin levels to the normal range. Long-acting forms of the medication are currently being investigated.

A number of limited studies have been published that report the achievement of pregnancy following successful induction of ovulation by the use of bromocriptine in 70-95% of patients with hyperprolactinemia. The spontaneous abortion rate in most studies of these gestations has been within the normal range of 16–20%. Discontinuation of therapy is recommended when conception is achieved. A review of 805 pregnancies associated with the therapeutic ingestion of bromocriptine during very early gestation failed to reveal any abnormalities in the rates of spontaneous abortion, multiple gestation, malformation, and prematurity. Perhaps the greatest concern for hyperprolactinemic patients who become pregnant is physiologic enlargement of the pituitary and the implied threat of tumor expansion if an adenoma is present. While several studies have reported uncomplicated pregnancies occurring in patients with microadenomas, consideration of po-
tential tumor growth remains, as indicated by the findings of Gemzell and Wang. In that study the course of pregnancy in patients with untreated macroadenomas was also followed. It was noted that 17% of the patients experienced symptoms of tumor expansion (headache, visual-field defect). These symptoms were distributed throughout all three trimesters; hence there is a need for visual-field surveillance throughout pregnancy. In contrast, the complication rate in those patients who had received previous surgical treatment for a prolactin-secreting pituitary tumor was significantly less. Thus, these results emphasize the necessity for a thorough evaluation in hyperprolactinemic women before administration of bromocriptine for induction of ovulation. Currently, bromocriptine is approved for use in hyperprolactinemia only in the absence of a demonstrable pituitary tumor.

References


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