

Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline

Shlomo Melmed, Felipe F. Casanueva, Andrew R. Hoffman, David L. Kleinberg, Victor M. Montori, Janet A. Schlechte, and John A. H. Wass

Cedars Sinai Medical Center (S.M.), Los Angeles, California 90048; University of Santiago de Compostela (F.F.C.), 15705 Santiago de Compostela, Spain; VA Palo Alto Health Care System (A.R.H.), Palo Alto, California 94304; New York University School of Medicine (D.L.K.), New York, New York 10016; Mayo Clinic Rochester (V.M.M.), Rochester, Minnesota 55905; University of Iowa (J.A.S.), Iowa City, Iowa 52242; and Churchill Hospital (J.A.H.W.), Headington, Oxford OX37LJ, United Kingdom

Objective: The aim was to formulate practice guidelines for the diagnosis and treatment of hyperprolactinemia.

Participants: The Task Force consisted of Endocrine Society-appointed experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society, The European Society of Endocrinology, and The Pituitary Society reviewed and commented on preliminary drafts of these guidelines.

Conclusions: Practice guidelines are presented for diagnosis and treatment of patients with elevated prolactin levels. These include evidence-based approaches to assessing the cause of hyperprolactinemia, treating drug-induced hyperprolactinemia, and managing prolactinomas in non-pregnant and pregnant subjects. Indications and side effects of therapeutic agents for treating prolactinomas are also presented. (*J Clin Endocrinol Metab* 96: 273–288, 2011)

METHOD OF DEVELOPMENT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the diagnosis and treatment of hyperprolactinemia a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based

guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop some of the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. *Cross-filled circles* indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Copyright © 2011 by The Endocrine Society

doi: 10.1210/jc.2010-1692 Received July 22, 2010. Accepted October 25, 2010.

Abbreviation: MRI, Magnetic resonance image or imaging.

Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered as suggestions.

Introduction and natural history

Prolactin synthesis and secretion by pituitary lactotroph cells is tonically suppressed by hypothalamic dopamine traversing the portal venous system to impinge on lactotroph D₂ receptors (3). Factors inducing prolactin synthesis and secretion include estrogen, thyrotropin-releasing hormone, epidermal growth factor, and dopamine receptor antagonists. The isolation of human prolactin in 1970 permitted development of RIAs (4, 5), which enabled identification of hyperprolactinemia as a distinct clinical entity and resulted in distinguishing prolactin-secreting tumors from nonfunctioning adenomas (6).

Prolactin acts to induce and maintain lactation of the primed breast. Nonpuerperal hyperprolactinemia is caused by lactotroph adenomas (prolactinomas), which account for approximately 40% of all pituitary tumors. Hyperprolactinemia may also develop due to pharmacological or pathological interruption of hypothalamic-pituitary dopaminergic pathways and is sometimes idiopathic. Regardless of etiology, hyperprolactinemia may result in hypogonadism, infertility, and galactorrhea, or it may remain asymptomatic (7–9). Bone loss occurs secondary to hyperprolactinemia-mediated sex steroid attenuation. Spinal bone density is decreased by approximately 25% in women with hyperprolactinemia (10) and is not necessarily restored with normalization of prolactin levels.

At autopsy, approximately 12% of pituitary glands are shown to harbor a clinically inapparent adenoma (11). The reported population prevalence of clinically apparent prolactinomas ranges from 6–10 per 100,000 to approximately 50 per 100,000 (12, 13). In an analysis of 1607 patients with medically treated hyperprolactinemia, the calculated mean prevalence was approximately 10 per 100,000 in men and approximately 30 per 100,000 in women, with a peak prevalence for women aged 25–34 yr

(14). However, the prevalence of ever-treated hyperprolactinemia was approximately 20 per 100,000 male patients and approximately 90 per 100,000 female patients. In women aged 25–34 yr, the annual incidence of hyperprolactinemia was reported to be 23.9 per 100,000 person years. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

Testing for hyperprolactinemia is straightforward, owing to the ease of ordering a serum prolactin measurement. Accordingly, an evidence-based, cost-effective approach to management of this relatively common endocrine disorder is required.

1.0. Diagnosis of Hyperprolactinemia

Recommendation

1.1. To establish the diagnosis of hyperprolactinemia, we recommend a single measurement of serum prolactin; a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress. We recommend against dynamic testing of prolactin secretion for the diagnosis of hyperprolactinemia (1|⊕⊕⊕⊕).

1.1. Evidence

Serum prolactin is assessed with the use of assays that yield accurate values, and assessment usually presents no challenges in the clinical setting. Assay-specific normal values are higher in women than in men and are generally lower than 25 μg/liter. When the World Health Organization Standard 84/500 is used, 1 μg/liter is equivalent to 21.2 mIU/liter (15, 16). Dynamic tests of prolactin secretion using TRH, L-dopa, nomifensine, and domperidone are not superior to measuring a single serum prolactin sample for the diagnosis of hyperprolactinemia (15, 16).

A prolactin level greater than 500 μg/liter is diagnostic of a macroprolactinoma (17). Although a prolactin level greater than 250 μg/liter usually indicates the presence of a prolactinoma, selected drugs, including risperidone and metoclopramide, may cause prolactin elevations above 200 μg/liter in patients without evidence of adenoma (18). Even minimal prolactin elevations may be consistent with the presence of a prolactinoma, but a non-prolactin-secreting mass should first be considered. However, substantial prolactin elevations can also occur with microadenomas.

1.1. Remarks

The initial determination of serum prolactin should avoid excessive venipuncture stress and can be drawn at any time of the day. A single determination is usually suffi-

cient to establish the diagnosis, but when in doubt, sampling can be repeated on a different day at 15- to 20-min intervals to account for possible prolactin pulsatility (15, 16).

Recommendation

1.2. In patients with asymptomatic hyperprolactinemia, we suggest assessing for macroprolactin (2|⊕⊕○○).

1.2. Evidence

Although 85% of circulating prolactin is monomeric (23.5 kDa), serum also contains a covalently bound dimer, “big prolactin,” and a much larger polymeric form, “big-big prolactin.” The term *macroprolactinemia* denotes the situation in which a preponderance of the circulating prolactin consists of these larger molecules. Antiprolactin autoantibodies may also be associated with macroprolactinemia (19). Larger prolactin forms (macroprolactin) are less bioactive, and macroprolactinemia should be suspected when typical symptoms of hyperprolactinemia are absent (20, 21). Many commercial assays do not detect macroprolactin. Polyethylene glycol precipitation is an inexpensive way to detect the presence of macroprolactin in the serum. Retrospective analyses of patients with hyperprolactinemia found that approximately 40% have macroprolactinemia (22, 23). Although a smaller proportion of patients with macroprolactinemia has signs and symptoms of hyperprolactinemia, galactorrhea is present in 20%, oligo/amenorrhea in 45%, and pituitary adenomas in 20% (22). Because macroprolactinemia is a common cause of hyperprolactinemia, routine screening for macroprolactin could eliminate unnecessary diagnostic testing and treatment (24). Because true hyperprolactinemia and macroprolactinemia cannot be reliably distinguished on clinical criteria alone, we suggest screening for macroprolactin in investigation of asymptomatic hyperprolactinemic subjects.

Recommendation

1.3. When there is a discrepancy between a very large pituitary tumor and a mildly elevated prolactin level, we recommend serial dilution of serum samples to eliminate an artifact that can occur with some immunoradiometric assays leading to a falsely low prolactin value (“hook effect”) (1|⊕⊕⊕⊕).

1.3. Evidence

For prolactinomas, serum prolactin levels generally parallel tumor size, and most patients with prolactin levels higher than 250 $\mu\text{g/liter}$ will harbor a prolactinoma. Macroprolactinomas (>10 mm in diameter) are typically associated with prolactin levels greater than 250 $\mu\text{g/liter}$. This association between serum prolactin levels and tumor

size is not always consistent, and tumor mass and prolactin levels may be dissociated (15, 16). One potential reason for the discrepancy is the hook effect, an assay artifact that may be observed when high serum prolactin concentrations saturate antibodies in the two-site immunoradiometric assay. The second (signaling) antibody binds directly to the excess prolactin remaining in the solution and, therefore, is less available to the prolactin already bound to the first (coupling) antibody. Therefore, artifactually low results are obtained. We recommend that when prolactin values are not as high as expected, the assay should be repeated after a 1:100 serum sample dilution to overcome a potential hook effect. Alternatively, after prolactin binding to the first antibody, a washout could be performed to eliminate excess unbound prolactin before adding the second antibody. Modestly elevated prolactin may occur in patients with large nonfunctioning adenomas due to decreased dopamine, which inhibits prolactin secretion from normal lactotrophs because of hypothalamic stalk dysfunction. When prolactin values are not as high as expected in a patient with a large macroadenoma, the assay should be repeated after a 1:100 serum sample dilution. This step will overcome a potential hook effect and will distinguish between a large prolactinoma and a large nonfunctioning adenoma. We recommend that this artifact be excluded in patients who have pituitary macroadenomas and apparently normal or mildly elevated prolactin levels (25, 26). Newer assays may obviate this problem, and alternative reference laboratories may be used (27).

2.0. Causes of hyperprolactinemia

Recommendation

2.1. We recommend excluding medication use, renal failure, hypothyroidism, and parasellar tumors in patients with symptomatic nonphysiological hyperprolactinemia (1|⊕⊕⊕⊕).

2.1. Evidence

A number of physiological states including pregnancy, breast-feeding, stress, exercise, and sleep can cause prolactin elevation, as can medications (Table 1) (28). Patients with renal insufficiency may have moderate hyperprolactinemia caused by impaired renal degradation of prolactin and altered central prolactin regulation (29, 30). In about one third of patients with kidney disease, hyperprolactinemia develops because of decreased clearance and enhanced production of the hormone (30, 31). Dialysis does not alter serum levels, but prolactin levels normalize after renal transplantation. Hyperprolactinemia may contribute to hypogonadal symptoms that accompany chronic kidney disease, and menses may return after bromocriptine therapy. Some patients with primary hy-

TABLE 1. Etiology of hyperprolactinemia

Physiological
Coitus
Exercise
Lactation
Pregnancy
Sleep
Stress
Pathological
Hypothalamic-pituitary stalk damage
Granulomas
Infiltrations
Irradiation
Rathke's cyst
Trauma: pituitary stalk section, suprasellar surgery
Tumors: craniopharyngioma, germinoma, hypothalamic metastases, meningioma, suprasellar pituitary mass extension
Pituitary
Acromegaly
Idiopathic
Lymphocytic hypophysitis or parasellar mass
Macroadenoma (compressive)
Macroprolactinemia
Plurihormonal adenoma
Prolactinoma
Surgery
Trauma
Systemic disorders
Chest—neurogenic chest wall trauma, surgery, herpes zoster
Chronic renal failure
Cirrhosis
Cranial radiation
Epileptic seizures
Polycystic ovarian disease
Pseudocyesis
Pharmacological
Anesthetics
Anticonvulsant
Antidepressants
Antihistamines (H ₂)
Antihypertensives
Cholinergic agonist
Drug-induced hypersecretion
Catecholamine depletor
Dopamine receptor blockers
Dopamine synthesis inhibitor
Estrogens: oral contraceptives; oral contraceptive withdrawal
Neuroleptics/antipsychotics
Neuropeptides
Opiates and opiate antagonists

Adapted from Melmed and Kleinberg (28).

pothyroidism have moderate hyperprolactinemia (6, 32, 33). Long-term or inadequately treated primary hypothyroidism can cause pituitary hyperplasia that may mimic a pituitary tumor. Hyperprolactinemia and enlargement of the pituitary gland due to thyroid failure can be reversed by treatment with L-thyroxine (34, 35), which may also decrease TRH drive. Because prolactin secretion is tonically inhibited by hypothalamic dopamine, disruption or compression of the pituitary stalk by a non-prolactin-secreting pituitary tumor or other parasellar mass will lead to hyperprolactinemia.

Patients with large nonfunctioning pituitary tumors, craniopharyngiomas, or granulomatous infiltration of the hypothalamus can develop hyperprolactinemia because of pituitary stalk compression or dopaminergic neuronal damage. In 226 patients with histologically confirmed nonfunctioning pituitary macroadenomas, a prolactin level greater than 94 $\mu\text{g/liter}$ reliably distinguished between prolactinomas and nonfunctioning adenomas (36).

Dopamine agonist therapy lowers prolactin levels and improves symptoms in patients with stalk compression, but it is not definitive therapy for a nonfunctioning adenoma. Fewer than 10% of patients with idiopathic hyperprolactinemia ultimately are found to harbor a microadenoma, and progression from a microadenoma to a macroadenoma is rare (37). Spontaneous normalization of prolactin levels occurs in approximately 30% of patients with idiopathic hyperprolactinemia (38). It is important to determine whether patients with hyperprolactinemia also have acromegaly (39) because prolactin is elevated in up to 50% of patients with GH-secreting tumors (6).

3.0. Management of drug-induced hyperprolactinemia

Recommendation

3.1. In a symptomatic patient with suspected drug-induced hyperprolactinemia, we suggest discontinuation of the medication for 3 d or substitution of an alternative drug, followed by remeasurement of serum prolactin (2 $\oplus\oplus\oplus\oplus$). Discontinuation or substitution of an antipsychotic agent should not be undertaken without consulting the patient's physician. If the drug cannot be discontinued and the onset of the hyperprolactinemia does not coincide with therapy initiation, we recommend obtaining a pituitary magnetic resonance image (MRI) to differentiate between medication-induced hyperprolactinemia and symptomatic hyperprolactinemia due to a pituitary or hypothalamic mass (1 $\oplus\oplus\oplus\oplus$).

3.1. Evidence

The most frequent cause of nontumoral hyperprolactinemia is medications. Neuroleptics/antipsychotic agents are the ones most commonly causing hyperprolactinemia (Table 1). Among patients taking typical antipsychotics (*e.g.* phenothiazines or butyrophenones), 40–90% have hyperprolactinemia, as do 50–100% of patients on risperidone (18, 40). With drug-induced hyperprolactinemia, prolactin levels increase slowly after oral administration, and it usually takes 3 d for levels to return to normal after drug discontinuation (41, 42). Although some patients with medication-induced hyperprolactinemia remain asymptomatic, women may develop galactorrhea and amenorrhea, and men may present with

low libido and erectile dysfunction (43–45). There are also reports of increased risk of bone loss in women with antipsychotic-induced hyperprolactinemia (46, 47).

Medication-induced hyperprolactinemia is usually associated with prolactin levels ranging from 25 to 100 $\mu\text{g/liter}$, but metoclopramide, risperidone, and phenothiazines can lead to prolactin levels exceeding 200 $\mu\text{g/liter}$ (45, 48). The mechanism is the dopamine antagonist effect of these medications. Variants of the dopamine D₂ receptor gene in patients taking this antagonist may exaggerate the hyperprolactinemic effect (40). In one group of 106 patients receiving antipsychotics, hyperprolactinemia was present in 81, 35, 29, and 38% of patients taking risperidone, olanzapine, ziprasidone, and typical antipsychotics, respectively (49).

Verapamil causes hyperprolactinemia in 8.5% of patients (50), presumably by blocking hypothalamic dopamine. Opiates and cocaine act through the μ -receptor (51–53) to cause mild hyperprolactinemia (54). The role of estrogen in causing hyperprolactinemia is controversial (50). Twelve to 30% of women taking higher estrogen-containing oral contraceptives may have a small increase in serum prolactin, but this finding is rarely an indication for therapy (55).

3.1. Values and preferences

Patients with drug-induced hyperprolactinemia must evaluate the merits of their current medication program with their physicians. Assessment should include the availability of alternative medications—such as antipsychotic agents with lower dopamine antagonist potency (56, 57) or aripiprazole, an atypical antipsychotic with both dopamine agonist and dopamine antagonist activity (58) that can lower prolactin and reverse hyperprolactinemia-related side effects (59)—and their relative merits and downsides, and the potential adverse impact of ongoing hyperprolactinemia.

Recommendation

3.2. We suggest that clinicians not treat patients with asymptomatic medication-induced hyperprolactinemia (2|⊕⊕⊕⊕). We suggest the use of estrogen or testosterone in patients with long-term hypogonadism (hypogonadal symptoms or low bone mass) related to medication-induced hyperprolactinemia (2|⊕⊕⊕⊕).

3.2. Evidence

No treatment is necessary in the asymptomatic patient with medication-induced hyperprolactinemia. If the drug cannot be discontinued or substituted and the patient has hypogonadal symptoms or low bone mass, estrogen or testosterone therapy should be considered (60).

Recommendation

3.3. We suggest that the first step in treatment of medication-induced hyperprolactinemia is to stop the drug if this is clinically feasible. If this is not possible, a drug with a similar action that does not cause hyperprolactinemia should be substituted, and if this is not feasible we suggest considering the cautious administration of a dopamine agonist in consultation with the patient's physician (2|⊕⊕⊕⊕).

3.3. Evidence

Whether to treat a patient who has antipsychotic-induced hyperprolactinemia with a dopamine agonist remains controversial. Some studies suggest that dopamine agonist therapy will normalize prolactin levels in only up to 75% of such patients but may lead to exacerbation of the underlying psychosis (61–64).

3.3. Values and preferences

In recommending against the use of dopamine agonists, we are placing a low value on avoiding the adverse consequences of hyperprolactinemia due to medications that cannot be replaced or discontinued, a low value on forgoing the potential benefits of dopamine agonists, and a high value on avoiding adverse effects of such therapy, including psychosis exacerbation.

4.0. Management of prolactinoma

Recommendation

4.1. We recommend dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas (1|⊕⊕⊕⊕). We recommend using cabergoline in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage (1|⊕⊕⊕⊕).

4.1. Evidence

A systematic review of the literature was commissioned by The Endocrine Society to evaluate the treatment effects of dopamine agonists in patients with hyperprolactinemia (Wang, A., R. Mullan, M. Lane, C. Prasad, N. Mwirigi, M. Fernandez, A. Bagatto, A. Hazem, F. Coto-Iglsias, J. Carey, M. Kovalaske, P. Erwin, G. Ghandhi, M. H. Murad, and V. M. Montori, unpublished data). In this review, consistent benefits on several patient-important outcomes and surrogate outcomes were demonstrated. The proportions (median; range) of patients with improved outcomes are: reduction in tumor size (62%; 20–100%), resolution of visual field defects (67%; 33–100%), resolution of amenorrhea (78%; 40–100%), resolution of infertility (53%; 10–100%), improvement of sexual function (67%;

6–100%), resolution of galactorrhea (86%; 33–100%), and normalization of prolactin level (68%; 40–100%). This evidence was mostly derived from observational studies that were frequently uncontrolled. Few, smaller comparative studies demonstrated imprecise estimates and had shorter follow-up. Despite this evidence being open to potential bias, the large treatment effect of dopamine agonists, the potential dose response effect (higher doses are frequently more effective), the biological plausibility, temporality between treatment and effect, consistency across studies, settings and methods, and coherence (consistency across agents within the same class) (66), all further the authors' confidence in the estimates of treatment effect for dopamine agonists in patients with hyperprolactinemia.

Prolactinomas are associated with galactorrhea, sexual dysfunction (6), and decreased bone density if gonadal steroids are reduced (67–70). When a prolactinoma is present, serum prolactin levels generally parallel the size of the tumor. However, a prolactinoma may be associated with any level of prolactin. Serum prolactin in patients with macroadenomas is usually higher than in patients with microadenomas. In 46 men with prolactinomas, serum prolactin was elevated at a mean 99 $\mu\text{g/liter}$ (range, 16–385 $\mu\text{g/liter}$) in 12 patients with microadenomas *vs.* a mean of 1415 $\mu\text{g/liter}$ (range, 387–67,900 $\mu\text{g/liter}$) in 34 patients with macroprolactinomas (71).

Among 271 women with hyperprolactinemia observed for up to 29 yr, 240 received dopamine agonists (including bromocriptine, cabergoline, and quinagolide). Prolactin levels normalized in 71% of these patients, and 80% exhibited total or partial tumor shrinkage (72). Of the 17 patients who underwent surgery, mostly for drug intolerance or resistance, 53% exhibited long-term normalization of prolactin levels without added medications.

In a placebo-controlled study, cabergoline treatment (0.125–1.0 mg twice weekly) for 12–24 months in patients harboring prolactin-secreting microadenomas resulted in normalization of prolactin levels in 95% of patients. Cabergoline restored menses in 82% of women with amenorrhea (73). In a prospective study of 26 treatment-naïve patients with macroprolactinomas, normoprolactinemia was achieved within 6 months in 81% of patients receiving 0.25–2 mg cabergoline weekly, and 92% exhibited significant tumor shrinkage (74). In a retrospective study of 455 patients, cabergoline normalized prolactin levels in 92% of patients with idiopathic hyperprolactinemia or a microprolactinoma and in 77% of 181 patients with macroadenomas (75).

Eighty percent of men harboring macroadenomas or microadenomas experience prolactin normalization after treatment with bromocriptine, cabergoline, or other dopamine agonists (71). In men, 6 months of treatment with cabergo-

line (0.5–1 mg twice weekly) restored nocturnal penile tumescence (76) and sperm count and motility (77, 78).

In a prospective dose-escalation study of 150 patients (122 women and 28 men) with 93 microadenomas and 57 macroadenomas, hyperprolactinemia normalized in 149 patients, irrespective of tumor size. Overall, control of hyperprolactinemia requires doses of cabergoline ranging from 0.25 to 3 mg/wk; however, occasional patients may require doses up to 11 mg/wk (79–82).

It is unclear why cabergoline is more effective than bromocriptine, but the greater efficacy may be explained by the fact that cabergoline has a higher affinity for dopamine receptor binding sites. Because the incidence of unpleasant side effects is lower with cabergoline, drug compliance may be superior for this medication (75). No clinical trials have directly compared the mass-reducing effects of different dopamine agonists. Nevertheless, results of various studies (83) indicate that bromocriptine decreases pituitary tumor size by approximately 50% in two thirds of patients, compared with a 90% decrease with cabergoline.

4.1. Values and preferences

In recommending cabergoline, we are placing a lower value on cost of treatment and a higher value on patient convenience and achieving reversal of hypogonadism.

4.1. Remarks

In patients who begin dopamine agonist therapy, follow-up includes: 1) periodic prolactin measurement starting 1 month after therapy to guide treatment intensification to achieve normal prolactin level and reversal of hypogonadism; 2) repeat MRI in 1 yr (or in 3 months in patients with macroprolactinoma, if prolactin levels continue to rise while patient is receiving dopaminergic agents, or if new symptoms, *e.g.* galactorrhea, visual disturbances, headaches, or other hormonal disorders, occur); 3) visual field examinations in patients with macroadenomas at risk of impinging the optic chiasm; and 4) assessment and management of comorbidities, *e.g.* sex-steroid-dependent bone loss, persistent galactorrhea in the face of normalized prolactin levels, and pituitary trophic hormone reserve.

Recommendation

4.2. We suggest that clinicians not treat asymptomatic patients harboring microprolactinomas with dopamine agonists (2|⊕○○○). We suggest treatment with a dopamine agonist or oral contraceptive in patients with amenorrhea caused by a microadenoma (2|⊕○○○).

4.2. Evidence

Microadenomas rarely grow (38). Hypogonadal premenopausal women with microadenomas who are not de-

sirous of pregnancy may be treated with oral contraceptives instead of dopamine agonist therapy. However, no controlled trials have compared these two options. Importantly, amenorrhea will not be an indicator of hyperprolactinemia recurrence in patients treated with oral contraceptives. Women with microadenomas who are not desirous of pregnancy may be treated with a dopamine agonist or oral contraceptives. No controlled trials have compared these two options, but oral contraceptives are less expensive and have fewer side effects. The effect of oral estrogen therapy on the growth of microadenomas has not been examined in a randomized controlled fashion. However, patients treated with oral contraceptives and estrogen/progesterone replacement for 2 yr have not shown an increase in tumor size (84, 85).

4.2. Values and preferences

This suggestion places a low value on any potential, yet highly uncertain benefit achieved by treatment and a high value on avoiding inconvenience, harm, and costs of medical or surgical therapy in these patients.

Recommendation

4.3. We suggest that with careful clinical and biochemical follow-up, therapy may be tapered and perhaps discontinued in patients who have been treated with dopamine agonists for at least 2 yr, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI (2|⊕○○○).

4.3. Evidence

Four recent studies (86–89) suggest that in a subset of patients, dopamine agonist withdrawal may be safely undertaken after 2 yr in patients who have achieved normoprolactinemia and significant tumor volume reduction. The risk of recurrence after withdrawal ranges from 26 to 69% (86, 89), and all studies have shown that recurrence is predicted by prolactin levels at diagnosis and by tumor size. Recurrences are most likely to occur in the year after withdrawal, and in one study the risk of recurrence was 18% per millimeter of tumor mass (89). Withdrawal of therapy has been associated with no evidence of tumor growth, but up to 28% of such patients may develop hypogonadism (89), suggesting the need for long-term surveillance and treatment of these patients.

4.3. Remarks

For patients who after 2 yr of therapy have achieved normal prolactin levels and no visible tumor remnant and for whom dopamine agonists have been tapered or discontinued, follow-up includes: 1) measurement of serum prolactin levels every 3 months for the first year and then

annually thereafter; and 2) MRI if prolactin increases above normal levels (87, 90). In women with microprolactinomas, it may be possible to discontinue dopaminergic therapy when menopause occurs. Surveillance for increasing size of the pituitary tumor should continue on a periodic basis.

5.0. Resistant and malignant prolactinoma

Recommendation

5.1. For symptomatic patients who do not achieve normal prolactin levels or show significant reduction in tumor size on standard doses of a dopamine agonist (resistant prolactinomas), we recommend that the dose be increased to maximal tolerable doses before referring the patient for surgery (1|⊕⊕⊕⊕).

5.1. Evidence

Responses to dopamine agonists are variable. The majority of patients with prolactinomas treated with standard doses of dopamine agonists respond with normalization of prolactin levels and a reduction in tumor size. However, some patients do not respond satisfactorily (91). Dopamine agonist resistance includes a failure to achieve a normal prolactin level on maximally tolerated doses of dopamine agonist and a failure to achieve a 50% reduction in tumor size (7). Furthermore, failure to restore fertility in patients receiving standard doses of dopamine agonist may also be reflective of treatment resistance. Some patients may have discordant responses, *i.e.* reduction in tumor size without normalization of prolactin levels and vice versa, and others may be partially resistant and require higher than typical doses of dopamine agonists to achieve a response. Dopamine agonist resistance differs from intolerance, where side effects of the agonists preclude their use.

The mechanism of dopamine agonist resistance is not completely understood. There is a decreased number of D₂ receptors expressed on resistant prolactinomas (92, 93), but this finding is not invariable (94). Dopamine receptor binding is normal, and no dopamine receptor mutation has been identified in prolactinomas. D₂ receptor isoform ratios may differ, and molecular alterations may occur downstream of the D₂ receptor. It is likely, therefore, that different mechanisms underlie dopamine agonist resistance in prolactinomas.

Microadenomas are less resistant to dopamine agonists than are macroadenomas. Ten percent of patients with microadenomas and 18% of patients with macroadenomas do not achieve normal prolactin levels on cabergoline (79, 80). Furthermore, men are more likely than women to be dopamine agonist resistant (95).

Increasing the cabergoline dose to as much as 11 mg/wk has been necessary in a few patients to overcome resistance. Although high doses of cabergoline may be necessary to overcome resistance, caution must be exhibited with protracted use of high-dose cabergoline because of the potential risk of cardiac valvular regurgitation. Patients with Parkinson's disease receiving at least 3 mg of cabergoline daily are at risk for moderate to severe cardiac valve regurgitation (96, 97). In contrast, six of seven studies analyzing cardiac valves in over 500 patients with prolactinomas receiving standard doses of cabergoline have shown no evidence of clinically significant valvular disease (98–103). The one study that did report a 57% incidence of tricuspid regurgitation in patients treated with cabergoline also noted significant tricuspid regurgitation in the control group (104).

5.1. Remarks

Dose increases should be stepwise and guided by prolactin levels. In patients who require very high doses for prolonged periods, echocardiography may be necessary to assess for valvular abnormalities. Although the precise dose and duration cannot be identified at this time, patients receiving typical doses of cabergoline (1–2 mg/wk) likely will not require regular echocardiographic screening.

Recommendation

5.2. We recommend that patients resistant to bromocriptine be switched to cabergoline (1|⊕⊕⊕⊕).

5.2. Evidence

Although we recommend cabergoline as first-line treatment for patients with prolactinoma, approximately 10% of patients are resistant to that drug. On the other hand, approximately 25% are resistant to bromocriptine (75, 82, 105), and 80% of these patients may achieve prolactin normalization on cabergoline (75, 80, 106). No clinical trials have directly compared the mass-reducing effects of different dopamine agonists. Nevertheless, results of various studies (83, 107) indicate that bromocriptine decreases pituitary tumor size by approximately 50% in two thirds of patients, whereas with cabergoline more than 90% of patients experience tumor shrinkage.

Recommendation

5.3. We suggest that clinicians offer transsphenoidal surgery to symptomatic patients with prolactinomas who cannot tolerate high doses of cabergoline or who are not responsive to dopamine agonist therapy. For patients who are intolerant of oral bromocriptine, intravaginal administration may be attempted. For patients who fail surgical

treatment or who harbor aggressive or malignant prolactinomas, we suggest radiation therapy (2|⊕○○○).

5.3. Evidence

There are no controlled studies regarding surgical outcomes in medically resistant tumors. However, 7–50% of surgically resected prolactin-secreting tumors recur (108, 109). Side effects of surgery, which are less commonly encountered with experienced pituitary surgeons, include hypopituitarism, diabetes insipidus, cerebrospinal fluid leak, and local infection (108).

Radiotherapy should be reserved for resistant or malignant prolactinomas. Normalization of hyperprolactinemia occurs in approximately one third of patients treated with radiation (7). Although radiotherapy may control tumor growth, it may require up to 20 yr for the maximal effect to be achieved and may never restore prolactin levels to normal. Radiation therapy is associated with side effects including hypopituitarism and, rarely, cranial nerve damage or second tumor formation (110).

Recommendation

5.4. In patients with malignant prolactinomas, we suggest temozolomide therapy (2|⊕○○○).

5.4. Evidence

A malignant prolactinoma is defined as one that exhibits metastatic spread within or outside the central nervous system. Malignant prolactinomas are rare, and approximately 50 have been described (111, 112). Histologically, it is not possible to differentiate between carcinoma and adenoma. There are currently no reliable pathological markers whereby the malignant potential of a prolactinoma can be predicted. Most commonly, a patient with an invasive prolactinoma has already undergone medical treatment, surgical treatment, and/or radiotherapy, often years before it was apparent that progression—and indeed metastasis—had occurred. Very uncommonly, a prolactinoma is clearly malignant *ab initio* (113).

Treatment of malignant tumors is difficult, and survival is usually approximately 1 yr (113). Surgery may be necessary to diminish the compressive effects of the lesion. Chemotherapy including procarbazine, vincristine, cisplatin, and etoposide has been used with little effect (111). Several case reports suggest the effective use of temozolomide, an alkylating agent (114, 115). Temozolomide has been shown to reduce prolactin levels and control tumor growth if tumor specimens do not express methylguanine-DNA methyltransferase (115–117), but the predictive value of this test has been tempered (118).

6.0. Management of prolactinoma during pregnancy

Recommendations

6.1. We recommend that women with prolactinomas be instructed to discontinue dopamine agonist therapy as soon as they discover that they are pregnant (1|⊕⊕⊕⊕).

In selected patients with macroadenomas who become pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm (1|⊕○○○).

6.1. Evidence

Because bromocriptine crosses the placenta (119), fetal drug exposure is likely for up to the first 4 wk after conception, a critical period for early organogenesis. In the more than 6000 pregnancies achieved and reported in women taking bromocriptine for hyperprolactinemia, the incidence of congenital malformations or abortions was not increased (120). Long-term follow-up of up to 9 yr in a limited number of children who were exposed to the drug *in utero* also showed no harmful effects (121). Cabergoline also appears to be safe when used to treat infertility in women with hyperprolactinemia, but there is far less published experience with this drug (122–125). In a prospective study of 85 women, of whom 80 achieved pregnancy while receiving cabergoline, the drug was withdrawn at 5 wk gestation, all babies were born healthy, and no mothers experienced tumor expansion (124). Therefore, the preponderance of evidence is that there will not be harm when the fetus is exposed to bromocriptine or cabergoline early in pregnancy (126). Quinagolide, on the other hand, has a poor safety profile in the relatively small number of pregnancies that have been reported, and it should not be prescribed to women desirous of becoming pregnant (127).

6.1. Values and preferences

Our recommendation to discontinue bromocriptine or cabergoline therapy in women who become pregnant places a relatively higher value on the potential risk of fetal harm from an exogenous drug and a relatively lower value on the risk of pituitary tumor growth.

Recommendation

6.2. In pregnant patients with prolactinomas, we recommend against performing serum prolactin measurements during pregnancy (1|⊕⊕⊕⊕).

6.2. Evidence

During pregnancy, serum prolactin levels increase 10-fold (128), reaching levels of 150 to 300 $\mu\text{g}/\text{liter}$ by term.

Moreover, the pituitary gland increases in volume more than 2-fold, primarily due to estrogen-stimulated increase in the number of lactotrophs (129). When dopamine agonists are discontinued at the start of pregnancy, serum prolactin levels increase, and subsequent increases in prolactin levels do not accurately reflect changes in tumor growth or activity. Moreover, serum prolactin levels may not increase during pregnancy in all patients with prolactinomas (130). Pregnancy may ameliorate antepartum hyperprolactinemia because postpartum serum prolactin levels are frequently lower than levels observed before conception; in some patients, hyperprolactinemia may resolve entirely after pregnancy (131, 132).

6.2. Values and preferences

Our recommendation to refrain from measuring serum prolactin during pregnancy in patients with prolactinomas places a high value on avoiding uninterpretable laboratory tests and unnecessary testing triggered by higher than normal prolactin levels.

Recommendation

6.3. We recommend against the use of routine pituitary MRI during pregnancy in patients with microadenomas or intrasellar macroadenomas unless there is clinical evidence for tumor growth such as visual field compromise (1|⊕⊕○○).

6.3. Evidence

There is a concern that macroprolactinomas may grow during pregnancy. Microadenomas are highly unlikely to expand during pregnancy (133, 134). Patients are told to discontinue dopamine agonist therapy when pregnancy is diagnosed; as a result, tumor shrinkage induced by these drugs may be reversed (135). High levels of estrogen that accompany pregnancy stimulate lactotroph hyperplasia in the normal gland (133, 136), and this physiological pituitary growth may cause the tumor to be displaced outside the sella. Finally, the high estrogen milieu may directly stimulate lactotroph tumor growth (137).

In general, microprolactinomas and macroprolactinomas that are localized to the sella do not undergo symptomatic growth during pregnancy. In a review of studies that included 457 pregnant women harboring microadenomas, 2.6% developed symptomatic tumor growth (7). In studies that examined tumor growth using imaging techniques, the risk of tumor growth was observed to be somewhat higher (4.5–5%) (7). Because the risk of symptomatic tumor growth is so low, pregnant patients with microadenomas may be followed by clinical examination during each trimester. The risk of symptomatic tumor growth in pregnant patients with macroadenomas, on the

other hand, is much higher. In those patients who had undergone debulking pituitary surgery or pituitary irradiation before pregnancy, the risk of symptomatic growth was only 2.8%, not substantially different from the microadenoma risk (120). However, in patients with macroadenoma who did not undergo surgery or irradiation before pregnancy, the risk of symptomatic pituitary tumor enlargement was 31% (7). The onset of new or worsening headache, or a change in vision, or both mandates the urgent performance of formal visual field testing and a pituitary MRI without the use of gadolinium.

Recommendation

6.4. We recommend that women with macroprolactinomas who do not experience pituitary tumor shrinkage during dopamine agonist therapy or who cannot tolerate bromocriptine or cabergoline be counseled regarding the potential benefits of surgical resection before attempting pregnancy (1|⊕⊕○○).

6.4. Evidence

Although some endocrinologists may recommend pituitary surgery to all patients with macroprolactinomas before attempting pregnancy (15), surgery can cause hypopituitarism, which may lead to the need for advanced reproductive technologies (*e.g.* ovulation induction with gonadotropins) to achieve pregnancy, as well as lifelong hormone replacement therapy.

Recommendation

6.5. We recommend formal visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas who experience severe headaches and/or visual field changes (1|⊕⊕○○).

6.5. Evidence

For most pregnant patients with prolactinomas, serial MRIs and formal visual field testing are not indicated in the absence of headaches or visual field changes. For patients who have macroadenomas and have not undergone prior pituitary surgery, it is prudent to undertake more frequent clinical examinations and formal visual field testing.

6.5. Values and preferences

Our recommendation to use the clinical examination rather than MRI to assess pregnant patients with prolactinoma on a routine basis places a high value on avoiding the potential risk to the fetus of the imaging procedure and a low value on precisely determining morphological changes to the tumor and surrounding structures. However, our recommendation to obtain an MRI if the patient develops severe headache or visual field abnormalities

places a high value on preventing permanent visual impairment and a lower value on preventing unsubstantiated risks of MRI harm to the fetus.

Recommendation

6.6. We recommend bromocriptine therapy in patients who experience symptomatic growth of a prolactinoma during pregnancy (1|⊕⊕○○).

6.6. Evidence

If the pituitary tumor does grow sufficiently to cause mass effect symptoms during pregnancy, therapeutic options include reinstatement of dopamine agonist therapy or surgical debulking of the adenoma. There are no controlled studies examining this question, and few data exist from case studies to evaluate potential harm from either approach. Continuous use of bromocriptine throughout pregnancy has been reported in only approximately 100 patients. This treatment does not appear to be harmful, although there was one reported case of undescended testis and one of talipes deformity (65, 120). Bromocriptine in divided doses is the recommended dopamine agonist of choice because of the larger published experience. In patients who cannot tolerate bromocriptine, cabergoline may be administered. If reinitiation of dopamine agonist therapy does not decrease tumor size and lead to improved symptoms, surgical resection may be indicated. There are no published data to assess a comparative risk of dopaminergic therapy and surgical resection during pregnancy; however, some endocrinologists prefer dopaminergic therapy in this circumstance. If the fetus is near term, it may be reasonable to induce delivery before neurosurgical intervention is undertaken.

6.6. Values and preferences

Our recommendation to use dopamine agonists to treat a growing prolactinoma during pregnancy places a higher value on avoiding the potential risk of surgery during pregnancy and a lower value on avoiding potential harm of these drugs to the fetus.

SUMMARY OF RECOMMENDATIONS

1.0. Diagnosis of hyperprolactinemia

1.1. To establish the diagnosis of hyperprolactinemia, we recommend a single measurement of serum prolactin; a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress. We recommend against dynamic testing of prolactin secretion for the diagnosis of hyperprolactinemia (1|⊕⊕⊕⊕).

1.2. In patients with asymptomatic hyperprolactinemia, we suggest assessing for macroprolactin (2|⊕⊕○○).

1.3. When there is a discrepancy between a very large pituitary tumor and a mildly elevated prolactin level, we recommend serial dilution of serum samples to eliminate an artifact that can occur with some immunoradiometric assays leading to a falsely low prolactin value (“hook effect”) (1|⊕⊕⊕⊕).

2.0. Causes of hyperprolactinemia

2.1. We recommend excluding medication use, renal failure, hypothyroidism, and pituitary and parasellar tumors in patients with symptomatic nonphysiological hyperprolactinemia (1|⊕⊕⊕⊕).

3.0. Management of drug-induced hyperprolactinemia

3.1. In a symptomatic patient with suspected drug-induced hyperprolactinemia, we suggest discontinuation of the medication for 3 d or substitution of an alternative drug, followed by remeasurement of serum prolactin (2|⊕⊕○○). Discontinuation or substitution of an antipsychotic agent should not be undertaken without consulting the patient’s physician. If the drug cannot be discontinued and the onset of the hyperprolactinemia does not coincide with therapy initiation, we recommend obtaining a pituitary MRI to differentiate between medication-induced hyperprolactinemia and symptomatic hyperprolactinemia due to a pituitary or hypothalamic mass (1|⊕○○○).

3.2. We suggest that clinicians not treat patients with asymptomatic medication-induced hyperprolactinemia (2|⊕⊕○○). We suggest use of estrogen or testosterone in patients with long-term hypogonadism (hypogonadal symptoms or low bone mass) related to medication-induced hyperprolactinemia (2|⊕○○○).

3.3. We suggest that the first step in treatment of medication-induced hyperprolactinemia is to stop the drug if this is clinically feasible. If this is not possible, a drug with a similar action that does not cause hyperprolactinemia should be substituted, and if this is not feasible, to consider the cautious administration of a dopamine agonist in consultation with the patient’s physician (2|⊕○○○).

4.0. Management of prolactinoma

4.1. We recommend dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas (1|⊕⊕⊕⊕). We recommend using cabergoline in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage (1|⊕⊕⊕⊕).

4.2. We suggest that clinicians not treat asymptomatic patients harboring microprolactinomas with dopamine agonists (2|⊕○○○). We suggest treatment with a dopamine agonist or oral contraceptives in patients with microadenomas who have amenorrhea (2|⊕○○○).

4.3. We suggest that with careful clinical and biochemical follow-up therapy may be tapered and perhaps discontinued in patients who have been treated with dopamine agonists for at least 2 yr, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI (2|⊕○○○).

5.0. Resistant and malignant prolactinoma

5.1. For symptomatic patients who do not achieve normal prolactin levels or show significant reduction in tumor size on standard doses of a dopamine agonist (resistant prolactinomas), we recommend that the dose be increased rather than referring the patient for surgery (1|⊕⊕⊕⊕).

5.2. We recommend that patients resistant to bromocriptine be switched to cabergoline (1|⊕⊕⊕⊕).

5.3. We suggest that clinicians offer transsphenoidal surgery to symptomatic patients with prolactinomas who cannot tolerate high doses of cabergoline or who are not responsive to dopamine agonist therapy. For patients who are intolerant of oral bromocriptine, intravaginal administration may be attempted. For patients who fail surgical treatment or who harbor aggressive or malignant prolactinomas, we suggest radiation therapy (2|⊕○○○).

5.4. For patients with malignant prolactinomas, we suggest temozolomide therapy (2|⊕○○○).

6.0. Management of prolactinoma during pregnancy

6.1. We recommend that women with prolactinomas be instructed to discontinue dopamine agonist therapy as soon as they discover that they are pregnant (1|⊕⊕○○).

In selected patients with macroadenomas who become pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm (1|⊕○○○).

6.2. In pregnant patients with prolactinomas, we recommend against performing serum prolactin measurements during pregnancy (1|⊕⊕⊕⊕).

6.3. We recommend against the use of routine pituitary MRI during pregnancy in patients with microadenomas or intrasellar macroadenomas unless there is clinical evi-

dence for tumor growth such as visual field compromise (1⊕⊕○○).

6.4. We recommend that women with macroprolactinomas who do not experience pituitary tumor shrinkage during dopamine agonist therapy or who cannot tolerate bromocriptine or cabergoline be counseled regarding the potential benefits of surgical resection before attempting pregnancy (1⊕⊕○○).

6.5. We recommend formal visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas who experience severe headaches and/or visual field changes (1⊕⊕○○).

6.6. We recommend bromocriptine therapy in patients who experience symptomatic growth of a prolactinoma during pregnancy (1⊕⊕○○).

Acknowledgments

The members of the Task Force thank The Endocrine Society's Clinical Guidelines Subcommittee and Clinical Affairs Core Committee and Council for their careful, critical review of earlier versions of this manuscript and their helpful comments and suggestions. We also thank the leadership of the European Society of Endocrinology and The Pituitary Society for their review and comments. In addition, we thank the many members of The Endocrine Society who reviewed the draft version of this manuscript when it was posted on the Society's website and who sent a great number of additional comments and suggestions, most of which were incorporated into the final version of the manuscript.

Address all correspondence and requests for reprints to: The Endocrine Society, 8401 Connecticut Avenue, Suite 900, Chevy Chase, MD 20815. E-mail: govtprof@endo-society.org. Telephone: 301-941-0200. Address all commercial reprint requests for orders 101 and more to: Walchli Tauber Group Inc. E-mail: Karen.burkhardt@wt-group.com. Address all reprint requests for orders for 100 or fewer to Society Services, Telephone: 301-941-0210, E-mail: societyservices@endo-society.org, or Fax: 301-941-0257.

The European Society of Endocrinology and The Pituitary Society sponsored this work.

Financial Disclosures of the Task Force: Shlomo Melmed (chair)—Financial or Business/Organizational Interests: Novartis, Ipsen; Significant Financial Interest or Leadership Position: International Society of Endocrinology, The Pituitary Society. Felipe F. Casanueva—Financial or Business/Organizational Interests: Pfizer, Novo Nordisk, Novartis; Significant Financial Interest or Leadership Position: International Society of Endocrinology, Pituitary Society. Andrew R. Hoffman—Financial or Business/Organizational Interests: Merck Serono, LG Life Sciences, Teva, Novartis, Theratechnologies, Pfizer; Significant Financial Interest or Leadership Position: Ambrx, Inc., Human Growth Foundation. David L. Kleinberg—Financial or Business/Organizational Interests: Novartis Pharmaceuticals, Eli Lilly, U.S. Department of Defense; Significant Financial Interest or

Leadership Position: The Pituitary Society. Victor M. Montori*—Financial or Business/Organizational Interests: Knowledge and Encounter Research Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared. Janet A. Schlechte—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared. John A. H. Wass—Financial or Business/Organizational Interests: Pfizer, Novo Nordisk, Novartis, Ipsen, Merck Serono; Significant Financial Interest or Leadership Position: The Pituitary Society.

*Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

References

- Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams Jr JW, Zaza S 2004 Grading quality of evidence and strength of recommendations. *BMJ* 328: 1490
- Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93:666–673
- Melmed S 2003 Mechanisms for pituitary tumorigenesis: the plastic pituitary. *J Clin Invest* 112:1603–1618
- Frantz AG, Kleinberg DL 1970 Prolactin: evidence that it is separate from growth hormone in human blood. *Science* 170:745–747
- Hwang P, Guyda H, Friesen H 1971 A radioimmunoassay for human prolactin. *Proc Natl Acad Sci USA* 68:1902–1906
- Kleinberg DL, Noel GL, Frantz AG 1977 Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. *N Engl J Med* 296: 589–600
- Gillam MP, Molitch ME, Lombardi G, Colao A 2006 Advances in the treatment of prolactinomas. *Endocr Rev* 27:485–534
- Klibanski A 2010 Clinical practice. Prolactinomas. *N Engl J Med* 362:1219–1226
- Schlechte JA 2003 Clinical practice. Prolactinoma. *N Engl J Med* 349:2035–2041
- Schlechte J, el-Khoury G, Kathol M, Walkner L 1987 Forearm and vertebral bone mineral in treated and untreated hyperprolactinemic amenorrhea. *J Clin Endocrinol Metab* 64:1021–1026
- Buurman H, Saeger W 2006 Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. *Eur J Endocrinol* 154:753–758
- Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirrowa MA, Beckers A 2006 High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab* 91:4769–4775
- Fernandez A, Karavitaki N, Wass JA 2010 Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)* 72:377–382
- Kars M, Souverein PC, Herings RM, Romijn JA, Vandenbroucke JP, de Boer A, Dekkers OM 2009 Estimated age- and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia. *J Clin Endocrinol Metab* 94:2729–2734
- Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A 2006 Guidelines of the Pituitary

- Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)* 65:265–273
16. Mancini T, Casanueva FF, Giustina A 2008 Hyperprolactinemia and prolactinomas. *Endocrinol Metab Clin North Am* 37:67–99, viii
 17. Vilar L, Freitas MC, Naves LA, Casulari LA, Azevedo M, Montenegro Jr R, Barros AI, Faria M, Nascimento GC, Lima JG, Nóbrega LH, Cruz TP, Mota A, Ramos A, Violante A, Lamounier Filho A, Gadelha MR, Czepielewski MA, Glezer A, Bronstein MD 2008 Diagnosis and management of hyperprolactinemia: results of a Brazilian multicenter study with 1234 patients. *J Endocrinol Invest* 31:436–444
 18. Kearns AE, Goff DC, Hayden DL, Daniels GH 2000 Risperidone-associated hyperprolactinemia. *Endocr Pract* 6:425–429
 19. Hattori N 2003 Macroprolactinemia: a new cause of hyperprolactinemia. *J Pharmacol Sci* 92:171–177
 20. Chahal J, Schlechte J 2008 Hyperprolactinemia. *Pituitary* 11:141–146
 21. Glezer A, Soares CR, Vieira JG, Giannella-Neto D, Ribela MT, Goffin V, Bronstein MD 2006 Human macroprolactin displays low biological activity via its homologous receptor in a new sensitive bioassay. *J Clin Endocrinol Metab* 91:1048–1055
 22. Donadio F, Barbieri A, Angioni R, Mantovani G, Beck-Peccoz P, Spada A, Lania AG 2007 Patients with macroprolactinaemia: clinical and radiological features. *Eur J Clin Invest* 37:552–557
 23. McKenna TJ 2009 Should macroprolactin be measured in all hyperprolactinaemic sera? *Clin Endocrinol (Oxf)* 71:466–469
 24. Gibney J, Smith TP, McKenna TJ 2005 The impact on clinical practice of routine screening for macroprolactin. *J Clin Endocrinol Metab* 90:3927–3932
 25. Barkan AL, Chandler WF 1998 Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the “high-dose hook effect”: case report. *Neurosurgery* 42:913–915; discussion 915–916
 26. Petakov MS, Damjanović SS, Nikolić-Durović MM, Dragojlović ZL, Obradović S, Gligorović MS, Simić MZ, Popović VP 1998 Pituitary adenomas secreting large amounts of prolactin may give false low values in immunoradiometric assays. The hook effect. *J Endocrinol Invest* 21:184–188
 27. Smith TP, Suliman AM, Fahie-Wilson MN, McKenna TJ 2002 Gross variability in the detection of prolactin in sera containing big big prolactin (macroprolactin) by commercial immunoassays. *J Clin Endocrinol Metab* 87:5410–5415
 28. Melmed S, Kleinberg D 2008 Anterior pituitary. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. *Williams textbook of endocrinology*. 11th ed. Philadelphia: Saunders Elsevier; 185–261
 29. Hou SH, Grossman S, Molitch ME 1985 Hyperprolactinemia in patients with renal insufficiency and chronic renal failure requiring hemodialysis or chronic ambulatory peritoneal dialysis. *Am J Kidney Dis* 6:245–249
 30. Lim VS, Kathpalia SC, Frohman LA 1979 Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: reversal after transplantation. *J Clin Endocrinol Metab* 48:101–107
 31. Sievertsen GD, Lim VS, Nakawatase C, Frohman LA 1980 Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. *J Clin Endocrinol Metab* 50:846–852
 32. Honbo KS, van Herle AJ, Kelleff KA 1978 Serum prolactin levels in untreated primary hypothyroidism. *Am J Med* 64:782–787
 33. Molitch ME 1992 Pathologic hyperprolactinemia. *Endocrinol Metab Clin North Am* 21:877–901
 34. Ahmed M, Banna M, Sakati N, Woodhouse N 1989 Pituitary gland enlargement in primary hypothyroidism: a report of 5 cases with follow-up data. *Horm Res* 32:188–192
 35. Keye WR, Yuen BH, Knopf RF, Jaffe RB 1976 Amenorrhea, hyperprolactinemia and pituitary enlargement secondary to primary hypothyroidism. Successful treatment with thyroid replacement. *Obstet Gynecol* 48:697–702
 36. Karavitaki N, Thanabalasingham G, Shore HC, Trifanescu R, Anson O, Meston N, Turner HE, Wass JA 2006 Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. *Clin Endocrinol (Oxf)* 65:524–529
 37. Sluijmer AV, Lappöhn RE 1992 Clinical history and outcome of 59 patients with idiopathic hyperprolactinemia. *Fertil Steril* 58:72–77
 38. Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A 1989 The natural history of untreated hyperprolactinemia: a prospective analysis. *J Clin Endocrinol Metab* 68:412–418
 39. Bonert VS, Melmed S 2006 Acromegaly with moderate hyperprolactinemia caused by an intrasellar macroadenoma. *Nat Clin Pract Endocrinol Metab* 2:408–412
 40. Calarge CA, Ellingrod VL, Acion L, Miller DD, Moline J, Tansey MJ, Schlechte JA 2009 Variants of the dopamine D2 receptor gene and risperidone-induced hyperprolactinemia in children and adolescents. *Pharmacogenet Genomics* 19:373–382
 41. Pollock A, McLaren EH 1998 Serum prolactin concentration in patients taking neuroleptic drugs. *Clin Endocrinol (Oxf)* 49:513–516
 42. Spitzer M, Sajjad R, Benjamin F 1998 Pattern of development of hyperprolactinemia after initiation of haloperidol therapy. *Obstet Gynecol* 91:693–695
 43. Cutler AJ 2003 Sexual dysfunction and antipsychotic treatment. *Psychoneuroendocrinology* 28(Suppl 1):69–82
 44. Knegtering H, van der Moolen AE, Castelein S, Kluiters H, van den Bosch RJ 2003 What are the effects of antipsychotics on sexual dysfunctions and endocrine functioning? *Psychoneuroendocrinology* 28(Suppl 2):109–123
 45. Smith S, Wheeler MJ, Murray R, O’Keane V 2002 The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. *J Clin Psychopharmacol* 22:109–114
 46. Ataya K, Mercado A, Kartaginer J, Abbasi A, Moghissi KS 1988 Bone density and reproductive hormones in patients with neuroleptic-induced hyperprolactinemia. *Fertil Steril* 50:876–881
 47. Misra M, Papakostas GI, Klibanski A 2004 Effects of psychiatric disorders and psychotropic medications on prolactin and bone metabolism. *J Clin Psychiatry* 65:1607–1618
 48. Meltzer HY, Fang VS 1976 Serum prolactin levels in schizophrenia-effect of antipsychotic drugs: a preliminary report. In: Sachar EJ, ed. *Hormones, behavior, and psychopathology*. New York: Raven Press
 49. Johnsen E, Kroken RA, Abaza M, Olberg H, Jørgensen HA 2008 Antipsychotic-induced hyperprolactinemia: a cross-sectional survey. *J Clin Psychopharmacol* 28:686–690
 50. Molitch ME 2005 Medication-induced hyperprolactinemia. *Mayo Clin Proc* 80:1050–1057
 51. Bart G, Borg L, Schluger JH, Green M, Ho A, Kreek MJ 2003 Suppressed prolactin response to dynorphin A1–13 in methadone-maintained versus control subjects. *J Pharmacol Exp Ther* 306:581–587
 52. Tolis G, Hickey J, Guyda H 1975 Effects of morphine on serum growth hormone, cortisol, prolactin and thyroid stimulating hormone in man. *J Clin Endocrinol Metab* 41:797–800
 53. Zis AP, Haskett RF, Albala AA, Carroll BJ 1984 Morphine inhibits cortisol and stimulates prolactin secretion in man. *Psychoneuroendocrinology* 9:423–427
 54. Mendelson JH, Mello NK, Teoh SK, Ellingboe J, Cochin J 1989 Cocaine effects on pulsatile secretion of anterior pituitary, gonadal, and adrenal hormones. *J Clin Endocrinol Metab* 69:1256–1260
 55. Luciano AA, Sherman BM, Chapler FK, Hauser KS, Wallace RB 1985 Hyperprolactinemia and contraception: a prospective study. *Obstet Gynecol* 65:506–510
 56. Kinon GJ, Gilmore JA, Liu H, Halbreich UM 2003 Prevalence of hyperprolactinemia in schizophrenic patients treated with conven-

- tional antipsychotic medications or risperidone. *Psychoneuroendocrinology* 28(Suppl 2):55–68
57. Volavka J, Czobor P, Cooper TB, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Lieberman JA 2004 Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychiatry* 65:57–61
 58. Lu ML, Shen WW, Chen CH 2008 Time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole. *Prog Neuropsychopharmacol Biol Psychiatry* 32:1978–1981
 59. Saitis M, Papazisis G, Katsigiannopoulos K, Kouvelas D 2008 Aripiprazole resolves amisulpride and ziprasidone-induced hyperprolactinemia. *Psychiatry Clin Neurosci* 62:624
 60. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM 2006 Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 91:1995–2010
 61. Cavallaro R, Cocchi F, Angelone SM, Lattuada E, Smeraldi E 2004 Cabergoline treatment of risperidone-induced hyperprolactinemia: a pilot study. *J Clin Psychiatry* 65:187–190
 62. Cohen LG, Biederman J 2001 Treatment of risperidone-induced hyperprolactinemia with a dopamine agonist in children. *J Child Adolesc Psychopharmacol* 11:435–440
 63. Smith S 1992 Neuroleptic-associated hyperprolactinemia. Can it be treated with bromocriptine? *J Reprod Med* 37:737–740
 64. Tollin SR 2000 Use of the dopamine agonists bromocriptine and cabergoline in the management of risperidone-induced hyperprolactinemia in patients with psychotic disorders. *J Endocrinol Invest* 23:765–770
 65. Konopka P, Raymond JP, Merceron RE, Seneze J 1983 Continuous administration of bromocriptine in the prevention of neurological complications in pregnant women with prolactinomas. *Am J Obstet Gynecol* 146:935–938
 66. Glasziou P, Chalmers I, Rawlins M, McCulloch P 2007 When are randomised trials unnecessary? Picking signal from noise. *BMJ* 334:349–351
 67. Antunes JL, Housepian EM, Frantz AG, Holub DA, Hui RM, Carmel PW, Quest DO 1977 Prolactin-secreting pituitary tumors. *Ann Neurol* 2:148–153
 68. Kleinberg DL, Frantz AG 1971 Human prolactin: measurement in plasma by in vitro bioassay. *J Clin Invest* 50:1557–1568
 69. Klibanski A, Greenspan SL 1986 Increase in bone mass after treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 315:542–546
 70. Melmed S, Braunstein GD, Chang RJ, Becker DP 1986 Pituitary tumors secreting growth hormone and prolactin. *Ann Intern Med* 105:238–253
 71. Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klibanski A 2000 Primary medical therapy of micro- and macroprolactinomas in men. *J Clin Endocrinol Metab* 85:3053–3057
 72. Berinder K, Stackenäs I, Akre O, Hirschberg AL, Hulting AL 2005 Hyperprolactinaemia in 271 women: up to three decades of clinical follow-up. *Clin Endocrinol (Oxf)* 63:450–455
 73. Webster J, Piscitelli G, Polli A, D'Alborton A, Falsetti L, Ferrari C, Fioretti P, Giordano G, L'Hermite M, Ciccarelli E 1992 Dose-dependent suppression of serum prolactin by cabergoline in hyperprolactinaemia: a placebo controlled, double blind, multicentre study. European Multicentre Cabergoline Dose-finding Study Group. *Clin Endocrinol (Oxf)* 37:534–541
 74. Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L, Lombardi G 2000 Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J Clin Endocrinol Metab* 85:2247–2252
 75. Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, Mahler C, Stevenaert A, Verlooy J, Raftopoulos C, Beckers A 1999 Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *J Clin Endocrinol Metab* 84:2518–2522
 76. De Rosa M, Zarrilli S, Vitale G, Di Somma C, Orio F, Tauchmanova L, Lombardi G, Colao A 2004 Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. *J Clin Endocrinol Metab* 89:621–625
 77. Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, Zarrilli S, Lombardi G 2004 Outcome of cabergoline treatment in men with prolactinoma: effects of a 24-month treatment on prolactin levels, tumor mass, recovery of pituitary function, and semen analysis. *J Clin Endocrinol Metab* 89:1704–1711
 78. De Rosa M, Ciccarelli A, Zarrilli S, Guerra E, Gaccione M, Di Sarno A, Lombardi G, Colao A 2006 The treatment with cabergoline for 24 month normalizes the quality of seminal fluid in hyperprolactinaemic males. *Clin Endocrinol (Oxf)* 64:307–313
 79. Di Sarno A, Landi ML, Cappabianca P, Di Salle F, Rossi FW, Pivonello R, Di Somma C, Faggiano A, Lombardi G, Colao A 2001 Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab* 86:5256–5261
 80. Ono M, Miki N, Kawamata T, Makino R, Amano K, Seki T, Kubo O, Hori T, Takano K 2008 Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J Clin Endocrinol Metab* 93:4721–4727
 81. Pascal-Vigneron V, Weryha G, Bosc M, Leclere J 1995 [Hyperprolactinemic amenorrhea: treatment with cabergoline versus bromocriptine. Results of a national multicenter randomized double-blind study]. *Presse Med* 24:753–757
 82. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF 1994 A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. *N Engl J Med* 331:904–909
 83. Molitch ME, Elton RL, Blackwell RE, Caldwell B, Chang RJ, Jaffe R, Joplin G, Robbins RJ, Tyson J, Thorner MO 1985 Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. *J Clin Endocrinol Metab* 60:698–705
 84. Corenblum B, Donovan L 1993 The safety of physiological estrogen plus progestin replacement therapy and with oral contraceptive therapy in women with pathological hyperprolactinemia. *Fertil Steril* 59:671–673
 85. Testa G, Vegetti W, Motta T, Alagna F, Bianchedi D, Carlucci C, Bianchi M, Parazzini F, Crosignani PG 1998 Two-year treatment with oral contraceptives in hyperprolactinemic patients. *Contraception* 58:69–73
 86. Biswas M, Smith J, Jadon D, McEwan P, Rees DA, Evans LM, Scanlon MF, Davies JS 2005 Long-term remission following withdrawal of dopamine agonist therapy in subjects with microprolactinomas. *Clin Endocrinol (Oxf)* 63:26–31
 87. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G 2003 Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 349:2023–2033
 88. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM 2010 Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. *J Clin Endocrinol Metab* 95:43–51
 89. Kharlip J, Salvatori R, Yenokyan G, Wand GS 2009 Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. *J Clin Endocrinol Metab* 94:2428–2436
 90. Klibanski A 2009 Dopamine agonist therapy in prolactinomas: when can treatment be discontinued? *J Clin Endocrinol Metab* 94:2247–2249
 91. Molitch ME 2003 Dopamine resistance of prolactinomas. *Pituitary* 6:19–27

92. Kukstas LA, Domec C, Bascles L, Bonnet J, Verrier D, Israel JM, Vincent JD 1991 Different expression of the two dopaminergic D2 receptors, D2415 and D2444, in two types of lactotroph each characterised by their response to dopamine, and modification of expression by sex steroids. *Endocrinology* 129:1101–1103
93. Pellegrini I, Rasolonjanahary R, Gunz G, Bertrand P, Delivet S, Jedynak CP, Kordon C, Peillon F, Jaquet P, Enjalbert A 1989 Resistance to bromocriptine in prolactinomas. *J Clin Endocrinol Metab* 69:500–509
94. Kovacs K, Stefaneanu L, Horvath E, Buchfelder M, Fahlbusch R, Becker W 1995 Prolactin-producing pituitary tumor: resistance to dopamine agonist therapy. Case report. *J Neurosurg* 82:886–890
95. Delgrange E, Daems T, Verhelst J, Abs R, Maiter D 2009 Characterization of resistance to the prolactin-lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. *Eur J Endocrinol* 160:747–752
96. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E 2007 Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 356:29–38
97. Zanettini R, Antonini A, Gatto G, Gentile R, Tesi S, Pezzoli G 2007 Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 356:39–46
98. Bogazzi F, Buralli S, Manetti L, Raffaelli V, Cigni T, Lombardi M, Boresi F, Taddei S, Salvetti A, Martino E 2008 Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia. *Int J Clin Pract* 62:1864–1869
99. Herring N, Szmigielski C, Becher H, Karavitaki N, Wass JA 2009 Valvular heart disease and the use of cabergoline for the treatment of prolactinoma. *Clin Endocrinol (Oxf)* 70:104–108
100. Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, Bax JJ, Pereira AM 2008 Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *J Clin Endocrinol Metab* 93:3348–3356
101. Lancellotti P, Livadariu E, Markov M, Daly AF, Burlacu MC, Betae D, Pierard L, Beckers A 2008 Cabergoline and the risk of valvular lesions in endocrine disease. *Eur J Endocrinol* 159:1–5
102. Vallette S, Serri K, Rivera J, Santagata P, Delorme S, Garfield N, Kahtani N, Beauregard H, Aris-Jilwan N, Houde G, Serri O 2009 Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. *Pituitary* 12:153–157
103. Wakil A, Rigby AS, Clark AL, Kallvikbacka-Bennett A, Atkin SL 2008 Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvular heart disease. *Eur J Endocrinol* 159:R11–14
104. Colao A, Di Somma C, Pivonello R, Faggiano A, Lombardi G, Savastano S 2008 Medical therapy for clinically non-functioning pituitary adenomas. *Endocr Relat Cancer* 15:905–915
105. Jaffe CA, Barkan AL 1992 Treatment of acromegaly with dopamine agonists. *Endocrinol Metab Clin North Am* 21:713–735
106. Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B, Annunziato L, Lombardi G 1997 Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. *J Clin Endocrinol Metab* 82:876–883
107. Freda PU, Andreadis CI, Khandji AG, Khoury M, Bruce JN, Jacobs TP, Wardlaw SL 2000 Long-term treatment of prolactin-secreting macroadenomas with pergolide. *J Clin Endocrinol Metab* 85:8–13
108. Losa M, Mortini P, Barzaghi R, Gioia L, Giovannelli M 2002 Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome. *J Clin Endocrinol Metab* 87:3180–3186
109. Serri O, Rasio E, Beauregard H, Hardy J, Somma M 1983 Recurrence of hyperprolactinemia after selective transphenoidal adenomectomy in women with prolactinoma. *N Engl J Med* 309:280–283
110. Brada M, Jankowska P 2008 Radiotherapy for pituitary adenomas. *Endocrinol Metab Clin North Am* 37:263–275, xi
111. Kaltsas GA, Nomikos P, Kontogeorgos G, Buchfelder M, Grossman AB 2005 Clinical review: diagnosis and management of pituitary carcinomas. *J Clin Endocrinol Metab* 90:3089–3099
112. Kars M, Roelfsema F, Romijn JA, Pereira AM 2006 Malignant prolactinoma: case report and review of the literature. *Eur J Endocrinol* 155:523–534
113. Popadić A, Witzmann A, Buchfelder M, Eiter H, Komminoth P 1999 Malignant prolactinoma: case report and review of the literature. *Surg Neurol* 51:47–54; discussion 54–55
114. Lim S, Shahinian H, Maya MM, Yong W, Heaney AP 2006 Temozolomide: a novel treatment for pituitary carcinoma. *Lancet Oncol* 7:518–520
115. McCormack AI, McDonald KL, Gill AJ, Clark SJ, Burt MG, Campbell KA, Braund WJ, Little NS, Cook RJ, Grossman AB, Robinson BG, Clifton-Bligh RJ 2009 Low O6-methylguanine-DNA methyltransferase (MGMT) expression and response to temozolomide in aggressive pituitary tumours. *Clin Endocrinol (Oxf)* 71:226–233
116. Hagen C, Schroeder HD, Hansen S, Hagen C, Andersen M 2009 Temozolomide treatment of a pituitary carcinoma and two pituitary macroadenomas resistant to conventional therapy. *Eur J Endocrinol* 161:631–637
117. Kovacs K, Horvath E, Syro LV, Uribe H, Penagos LC, Ortiz LD, Fadul CE 2007 Temozolomide therapy in a man with an aggressive prolactin-secreting pituitary neoplasm: morphological findings. *Hum Pathol* 38:185–189
118. Bush ZM, Longtine JA, Cunningham T, Schiff D, Jane Jr JA, Vance ML, Thorner MO, Laws Jr ER, Lopes MB 28 July 2010 Temozolomide treatment for aggressive pituitary tumors: correlation of clinical outcome with O6-methylguanine methyltransferase (MGMT) promoter methylation and expression. *J Clin Endocrinol Metab* 95:E280–E290
119. Bigazzi M, Ronga R, Lancranjan I, Ferraro S, Branconi F, Buzzoni P, Martorana G, Scarselli GF, Del Pozo E 1979 A pregnancy in an acromegalic woman during bromocriptine treatment: effects on growth hormone and prolactin in the maternal, fetal, and amniotic compartments. *J Clin Endocrinol Metab* 48:9–12
120. Molitch ME 2006 Pituitary disorders during pregnancy. *Endocrinol Metab Clin North Am* 35:99–116, vi
121. Raymond JP, Goldstein E, Konopka P, Leleu MF, Merceron RE, Loria Y 1985 Follow-up of children born of bromocriptine-treated mothers. *Horm Res* 22:239–246
122. Christin-Maitre S, Delemer B, Touraine P, Young J 2007 Prolactinoma and estrogens: pregnancy, contraception and hormonal replacement therapy. *Ann Endocrinol (Paris)* 68:106–112
123. Colao A, Abs R, Bárcena DG, Chanson P, Paulus W, Kleinberg DL 2008 Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. *Clin Endocrinol (Oxf)* 68:66–71
124. Ono M, Miki N, Amano K, Kawamata T, Seki T, Makino R, Takano K, Izumi S, Okada Y, Hori T 2010 Individualized high-dose cabergoline therapy for hyperprolactinemic infertility in women with micro- and macroprolactinomas. *J Clin Endocrinol Metab* 95:2672–2679
125. Robert E, Musatti L, Piscitelli G, Ferrari CI 1996 Pregnancy outcome after treatment with the ergot derivative, cabergoline. *Reprod Toxicol* 10:333–337
126. Bronstein MD 2005 Prolactinomas and pregnancy. *Pituitary* 8:31–38
127. Webster J 1996 A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Saf* 14:228–238
128. Rigg LA, Lein A, Yen SS 1977 Pattern of increase in circulating prolactin levels during human gestation. *Am J Obstet Gynecol* 129:454–456
129. Gonzalez JG, Elizondo G, Saldivar D, Nanez H, Todd LE, Villarreal

- JZ 1988 Pituitary gland growth during normal pregnancy: an in vivo study using magnetic resonance imaging. *Am J Med* 85:217–220
130. Divers Jr WA, Yen SS 1983 Prolactin-producing microadenomas in pregnancy. *Obstet Gynecol* 62:425–429
131. Crosignani PG, Mattei AM, Severini V, Cavioni V, Maggioni P, Testa G 1992 Long-term effects of time, medical treatment and pregnancy in 176 hyperprolactinemic women. *Eur J Obstet Gynecol Reprod Biol* 44:175–180
132. Jeffcoate WJ, Pound N, Sturrock ND, Lambourne J 1996 Long-term follow-up of patients with hyperprolactinaemia. *Clin Endocrinol (Oxf)* 45:299–303
133. Kupersmith MJ, Rosenberg C, Kleinberg D 1994 Visual loss in pregnant women with pituitary adenomas. *Ann Intern Med* 121:473–477
134. Molitch ME 1999 Medical treatment of prolactinomas. *Endocrinol Metab Clin North Am* 28:143–169, vii
135. Johnston DG, Prescott RW, Kendall-Taylor P, Hall K, Crombie AL, Hall R, McGregor A, Watson MJ, Cook DB 1983 Hyperprolactinemia. Long-term effects of bromocriptine. *Am J Med* 75: 868–874
136. Scheithauer BW, Sano T, Kovacs KT, Young Jr WF, Ryan N, Randall RV 1990 The pituitary gland in pregnancy: a clinicopathologic and immunohistochemical study of 69 cases. *Mayo Clin Proc* 65:461–474
137. Heaney AP, Fernando M, Melmed S 2002 Functional role of estrogen in pituitary tumor pathogenesis. *J Clin Invest* 109: 277–283



Refer a new active member and you could receive a \$10 Starbucks Card when they join.

www.endo-society.org/referral