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

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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 nonpregnant 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

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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 D_2 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 μg/liter will harbor a prolactinoma. Macroprolactinomas (>10 mm in diameter) are typically associated with prolactin levels greater than 250 μg/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 μg/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|⊕⊕○○). 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|⊕○○○).

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 μg/liter, but metoclopramide, risperidone, and phenothiazines can lead to prolactin levels exceeding 200 μg/liter (45, 48). The mechanism is the dopamine antagonist effect of these medications. Variants of the dopamine D_2 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-Iglysias, 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 μg/liter (range, 16–385 μg/liter) in 12 patients with microadenomas *vs.* a mean of 1415 μg/liter (range, 387–67,900 μg/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-naive 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 cabergoline (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 D_2 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. D_2 receptor isoform ratios may differ, and molecular alterations may occur downstream of the D_2 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, cisplatinum, 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 μg/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 reinstitution 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|⊕⊕◯◯).

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