Consensus

Diagnosis and management of hyperprolactinemia: expert consensus – French Society of Endocrinology

Diagnostic et prise en charge des hyperprolactinémies – Consensus d’experts de la Société française d’endocrinologie (SFE)

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At the SFE congress in October 2005, a session was devoted to a frequently encountered question in endocrinology: diagnosing and managing hyperprolactinemia. This is the second set of recommendations in the series of consensus, the first having dealt with “management of asymptomatic primary hyperparathyroidism” in 2004.

The symptoms caused by hyperprolactinemia frequently prompt patients to consult in general practices, endocrinology, gynecology or reproduction medicine. There are many aspects in the disorder that are controversial, and physicians often face questions in their daily practice for which they would like a consensus to follow, or at least a well-documented review on which to base their answers (1).

1. Hyperprolactinemia

Prolactin is secreted by lactotroph cells in the anterior lobe of the pituitary gland. It is permanently inhibited by hypothalamic dopamine. When the inhibition is lifted, whether pharmaceutically or by a lesion, prolactin secretion increases, resulting in hyperprolactinemia. As opposed to pituitary stimulins, prolactin directly affects the target tissue in charge of the final biological action, i.e. lactation in this case. In the mammary gland, prolactin is essential to prepare and stimulate lactation. Prolactin also acts on hypothalamic neurons that secrete Gonadotropin Releasing Hormone (GnRH). Hyperprolactinemia results in hypogonadism by altering the pulsatile secretion of GnRH, which in turn inadequately stimulates the production of gonadotrophic hormones (FSH and LH).

Hyperprolactinemia is a frequently encountered clinical situation, accounting for 20 to 25% of referrals for secondary amenorrhea. It is defined by the elevation of serum prolactin beyond the upper limit (figures vary according to assaying methods) usually 15-25 ng/ml (or approximately 300-500 mU/l). The average serum prolactin levels are slightly lower in men and in menopausal women that are not treated by estrogen stimulators.

2. When Should Prolactin be Measured?

Prolactin levels should mainly be measured when symptoms of hyperprolactinemia appear or in disorders caused by pituitary malfunction such as certain types of infertility or growth retardation [2–5].

2.1. When Signs of Hyperprolactinemia Appear

The first sign of elevated prolactin in premenopausal women is usually a disturbed menstrual cycle: secondary amenorrhea, oligo spaniomenorrhea (less frequent and less abundant period). Disturbances are masked in women treated with hormonal contraceptives, and can only reveal once contraceptives are stopped. This constitutes the classical post-contraception amenorrhea. Galactorrhea can also be a sign of excess prolactin, though in most cases prolactin levels are normal. Sexual disturbances such as a decreased libido, dyspar-

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euny due to low estrogen levels are frequently associated. Prolonged low estrogen levels can lead to osteopenia, more often discovered by systematic bone assessment than by pathological fractures [6]. In postmenopausal women galactorrhea is a rare finding because of endogenous hypoestrogenemia and because excess prolactin produces very few signs. In young girls, primary amenorrhea is the consequence of hyperprolactinemia, and depending on the age at which the disorder occurs, it can cause puberty retardation or interruption.

The functional signs of high serum prolactin in men mainly affect the sexual realm: low libido, erectile dysfunction [7–9]. Clinically, signs of gynecomasty can be seen, more rarely galactorrhea. Serum prolactin levels should be included in routine hormonal measurement when gynecomasty is seen in teenage boys, even though it is often normal in this setting. Elevated prolactin in younger boys causes puberty retardation or interruption. Growth retardation due to low levels of growth hormone should also lead to investigate prolactin levels: when prolactin is elevated, a hypothalamopituitary mass syndrome (craniopharyngioma, germinoma, possibly macroprolactinoma) can be suspected.

Routine hormonal measurement for infertility is another particular case where prolactin measurement should be included, in particular if menstrual cycles are disturbed in the woman or libido is decreased in the man.

2.2. When a tumoral pituitary syndrome is found

Elevated serum prolactin levels can be associated with intracranial tumors when the pituitary stem is compressed by a hypophyseal lesion (non-secreting adenoma) or a suprasellar lesion (craniopharyngioma, meningioma, germinoma) or when there is a prolactin-secreting (prolactinoma) or a mixed-secretion adenoma (frequently growth hormone and prolactin). Typical symptoms of a pituitary or supra-pituitary mass include headaches and visual disorders.

Headaches due to a pituitary adenoma usually predominate in the forehead, possibly in the orbits or in both temples. They are not pulsatile, and their intensity is not directly correlated with tumoral size. Also note that because of the many factors involved, headaches are not always directly linked to adenomas and may recur after adenomas have been treated.

Visual disorders due to compression of the chiasm are often perceived late in the development of the disorder by patients, as they affect the visual field before affecting sight. Typically, a bitemporal hemianopsia is found, but every variation of the disorder has been reported. Disturbances should be assessed by campimetry. They require rapidly effective treatment, be it medical or surgical.

2.3. When Assessing a Pituitary Disorder

Regardless of the pituitary disorder suspected, prolactin measurement provides crucial information on one of the 5 families of pituitary hormones. In macroadenomas (over 10 mm), moderately elevated prolactin levels (under 100-150 or even 200 ng/ml, or 2000 to 4000 mUI/l) suggests a compression of the pituitary stem rather than a prolactinoma. In this type of situation, levels of serum prolactin are well-correlated with the volume of prolactinomas, therefore a large pituitary lesion with moderately elevated prolactin levels is more likely to be a non-functional adenoma (usually gonadotrophic), a meningioma, a craniopharyngioma or other masses that do not secrete prolactin but that interfere with the negative regulation of prolactin-secreting cells. In acromegaly, as in every case of pituitary adenoma, it is particularly important to detect a mixed secretion [10]. In an increasing number of situations, pituitary lesions are chance discoveries on brain images (scanner or Magnetic Resonance Imaging) acquired for reasons that have nothing to do with a pituitary disorder (after head trauma for example). When these “pituitary incidentalomas” are discovered, prolactin measurement should be systematic since prolactin microadenomas are the most frequent secreting pituitary adenomas.

3. Etiology of Hyperprolactinemia

3.1. Hyperprolactinemia has Many Etiologies

The first causes to eliminate are physiological, the most common being pregnancy. Slightly elevated prolactin can be stress-related, and when suspected, prolactin should be measured when the patient is resting; this situation does not require multiple measurements via a catheter. Practically speaking, blood samples do not need to be scheduled according to the cycle, the time of the day (but the end of the night should be avoided) or meals. Because of the many possible causes for fluctuation, we do recommend, however, that when moderately elevated prolactin levels are found (less than 5 times the normal levels), a second measure be made on another blood sample, making certain that no medication causing hyperprolactinemia has been taken, and using a different kit when possible (in a different laboratory) to eliminate artifacts due to heavy forms (see below), before any other diagnostic measure is taken.

At this point it is crucial to systematically seek out whether drugs that elevate prolactin levels have been taken (Table 1). Neuroleptics have occasionally been known to increase prolactin levels beyond 10 times the upper normal levels. Interrupting a treatment that causes hyperprolactinemia should be discussed with the patient’s physician, specialists, and the patient himself. In some cases (neuroleptics for example) a drug that does not increase prolactin levels as dramatically can replace the initial treatment (Table 1). When the treatment can not be interrupted, a pituitary MRI is the only means to ensure that elevated prolactin levels are not due to a tumor. It is unnecessary to interrupt oral contraception or hormone substitution in most cases. When the incriminated drug can be stopped, prolactin assay should be delayed: after a few hours for antiemetic drugs, a few days for non-retard forms of neuroleptics, and a few weeks for retard neuroleptics, just to mention a few.
Table 1
List of main drugs inducing hyperprolactinemia
Tableau 1
Liste des principaux médicaments hyperprolactinémiants

<table>
<thead>
<tr>
<th>Neuroleptics</th>
<th>Degree of hyperprolactinemia</th>
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<tbody>
<tr>
<td>Phenothiazine</td>
<td>+++</td>
</tr>
<tr>
<td>Butyrophenone</td>
<td>+++</td>
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<tr>
<td>Thioxantheme</td>
<td>+++</td>
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<tr>
<td>Benzamide</td>
<td>+++</td>
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<tr>
<td>Risperidone</td>
<td>+++</td>
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<tr>
<td>Veralipride</td>
<td>+</td>
</tr>
<tr>
<td>Loxapine</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>0</td>
</tr>
<tr>
<td>Arripiprazole</td>
<td>0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td>Pimozide</td>
<td>+</td>
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<th>Antidepressors</th>
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<tbody>
<tr>
<td>Tricyclics</td>
<td>+</td>
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<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>a few reported cases</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>a few reported cases</td>
</tr>
<tr>
<td>Citaprolam</td>
<td>+/-</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>+/-</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+/-</td>
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<tr>
<td>Venlafaxine</td>
<td>+/-</td>
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<tr>
<th>Treatment of nausea and vomiting</th>
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</thead>
<tbody>
<tr>
<td>Benzamide</td>
<td>+++</td>
</tr>
<tr>
<td>Phenothiazine-derived drugs</td>
<td>+++</td>
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</tbody>
</table>

<table>
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<tr>
<th>H2 antihistaminic</th>
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<tbody>
<tr>
<td>Cimetidine (Tagamet®)</td>
<td>+</td>
</tr>
<tr>
<td>Ranitidine (Azantac®)</td>
<td>+</td>
</tr>
<tr>
<td>Famotidine (Pepcidac®)</td>
<td>a few reported cases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-hypertensive drugs</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Verapamil (Isotpine®, Tarka LP®)</td>
<td>++</td>
</tr>
<tr>
<td>Methyl dopa (Aldomet®)</td>
<td>+</td>
</tr>
<tr>
<td>Reserpine</td>
<td>+</td>
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<table>
<thead>
<tr>
<th>Other</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>+</td>
</tr>
<tr>
<td>Methadone</td>
<td>+</td>
</tr>
<tr>
<td>High dose estrogens</td>
<td>+</td>
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</table>

If elevated prolactin does not have any effect on gonads or if cycle disorders can be explained by other mechanisms, we recommend investigating macroprolactin levels, where antipro lactin autoantibodies form a complex with prolactin. This cause should also be sought out when MRIs are normal or inconclusive, when there is a discordance in response to medical or surgical treatments, or when prolactin levels vary dramatically from one blood test to another in a given patient [11–14]. Control serum prolactin measurement with a kit that is less sensitive to macroprolactin levels can sometimes help orient the diagnosis. The gold standard method is chromatography. But it is long and costly, and can be replaced, at least for screening purposes, by polyethylene glycol precipitation methods, on the condition that the method has been validated by the laboratory that performs it. A method for measuring macroprolactinemia should be available in referral centers for pituitary disorders [15–22].

Dynamic testing should not be used as a first line test. It should not guide the decision to ask for an MRI. It can be useful in some cases [23–25], in particular when the MRI is inconclusive: insufficient stimulation (<100%) after TRH or metoclopramide suggests the presence of a microprolactinoma, as opposed to cases where response to stimulation is normal, a situation that is exceptionally encountered in prolactinomas but that can be seen with artifactual images of lesions or with lesions such as certain intrapituitary cysts.

Since the cost-benefice ratio of systematic TSH measurement is inconclusive, we recommend that TSH be measured at least in cases where there are signs of hypothyroidism [26, 27], or if a hyperplastic pituitary is suspected on the MRI. Classically, a kidney work is requested [28] and possibly a liver work up to eliminate chronic kidney or liver failure that can both cause hyperprolactinemia by decreasing the metabolic clearance of prolactin. But in such situations the underlying disorder is usually known and can be more simply discovered through patient interview. When persisting hyperprolactinemia is found with levels that are beyond twice the upper limit in a patient with a polycystic ovary syndrome (PCOS), once macroprolactin has been eliminated, an MRI should be carried out. But PCOS as a cause for hyperprolactinemia (possibly via relative hyperestrogenemia) is an elimination diagnosis [29].

If, once the entire diagnosis process has been walked through, confirmed hyperprolactinemia has not yet found an underlying cause, a pituitary MRI should be performed [30, 31]. Coronal T2 and T1-weighted sections before and after injection are usually enough to identify microadenomas. Dynamic MRI with gadolinium injection should give rise to cautious interpretation as it is prone to yielding false positives. Sections in the frontal and lateral directions are required in cases of mass syndrome. In prolactinomas, prolactin concentrations correlate fairly well with adenoma volume. When prolactin levels are moderately elevated despite a large mass, hyperprolactinemia may be due to stem compression by a non lactotropic lesion, or to a hook effect [32,33]. This assay phenomenon causes prolactin levels to be found moderately elevated when they are, in fact, extremely elevated. Dilutions should be requested before assaying (1/100 times for example) when a hook effect is suspected.

4. Prolactinomas

4.1. Different Types of Prolactinomas

Pituitary adenomas that secrete prolactin are called “prolac tinomas” and are the most frequently encountered pituitary tumors [34]. They are classified according to their size as determined by an MRI or a CAT-scan: microadenomas have a diameter that is smaller than the arbitrary threshold of 10 mm, while macroadenomas are 10 mm or more [35–39]. Their treatment has been modified over the past few years [40].

Prolactin adenomas are for the greatest part benign, monoclonal in origin. Occasionally, a prolactinoma can be aggressive or locally invasive, compressing the neighboring structures. This type of adenoma is more frequent in men than in women [41]. Malignant prolactinomas that are treatment resistant and that disseminate within or beyond the central ner-
vous system have been described, but they are extremely rare. Mixed adenomas that secrete both growth hormone and prolactin are well-documented. Patients with this disorder usually have signs of acromegaly and of hyperprolactinemia. Before any treatment is begun for a prolactinoma, growth hormone levels should be checked at the slightest doubt to ensure that the tumor does not secrete both hormones. A potentially mixed adenoma should particularly be sought in cases of macroprolactinoma.

4.2. Prolactinoma and Pregnancy

In the course of a normal pregnancy, estrogens stimulate the production and secretion of prolactin, as well as lactotroph cell proliferation. Thus the pituitary is physiologically hyperplastic in pregnant women [42].

In microprolactinomas, treatment with dopaminergic agonists restores fertility in over 90% of cases. Surgical treatment may be required when the tumor is resistant, or the patient is intolerant to the treatment, or more simply when he/she requests surgery. Bromocriptine is the dopaminergic agonist that has been the most used during pregnancy. It does not carry any known risks for the fetus or the mother. As for the other dopaminergic agonists, no teratogenic cases have been reported during pregnancy. Quinagolide and especially cabergoline are often better tolerated and more efficient, and are in the process of becoming the standard first line treatment, though we have less experience with them and should therefore use them with the caution that is due, as noted in the French legal mentions of these drugs. Quinagolide and especially cabergolene can be used when there is a pregnancy project if the benefit in legal terms justifies the use of these drugs. Quinagolide and especially cabergoline can be used when there is a pregnancy project if the benefit in terms of efficiency and tolerance is deemed important [43–49]. Complications due to enlarging microprolactinomas are exceptionally rare during pregnancy (0.5–2%). Consequently dopamine agonist treatments can be interrupted as soon as pregnancy is diagnosed, except in particular cases. We do not recommend measuring prolactin during pregnancy (normal values can reach over 300 ng/ml toward the end of pregnancy), nor scheduling systematic visual field tests or MRIs unless there are headaches or visual defects.

As for macroprolactinomas, they expand in 15 to 30% of cases during pregnancy. This in itself is enough to suggest that dopamine agonists should be continued during pregnancy. Treatment interruption should only be recommended when there is no tumoral risk, in particular when there is no developing suprasellar tumor that might endanger the optic pathways. Visual field should be tested every 2-to-3 months, and an MRI without injection performed if tumoral signs appear (to be avoided during the first trimester). Patients should be followed by a specialist (endocrinologist), along with a general practitioner and an obstetrician.

In the post-partum period, breast feeding is possible and may even cause a remission in hyperprolactinemia. In cases of macroadenoma, breast-feeding is contraindicated if the agonist treatment is continued or needs to be resumed quickly, such as in cases of suprasellar extension. In certain cases where macroadenomas –to be discussed individually– did not cause any complication during pregnancy, resuming the agonist treatment can be delayed to allow for breast feeding. This can be done in enclosed macroadenomas, for example.

4.3. Contraception and Prolactinoma

Data regarding this point is limited in literature. The progression of hyperprolactinemia under oral estroprogestative contraceptives does not seem to modify prolactin levels or imaging. The main risk with estroprogestatives is that they may mask hyperprolactinemia [50]. Micro- and macropregestative contraception (in women over 40) cause tolerance problems but their effect on prolactin levels have not been investigated. A contraceptive pill containing less than 35 μg of ethynil estradiol can be prescribed to certain patients with a prolactin microadenoma if they are followed more closely. Estroprogestative tolerance should be assessed by measuring prolactin levels before and 3 months after beginning the treatment. Some authors suggest that the size of the adenoma should also be checked with an MRI within the first year of treatment to ensure that it does not cause tumoral growth.

5. Radical Treatment of Prolactinomas

5.1. Surgery

Dopamine agonists are so efficient in controlling prolactin hypersecretion and reducing tumoral mass in the vast majority of enclosed or invasive adenomas that surgery should not be the first-line treatment of prolactinoma [51–53]. It has not been demonstrated that dopamine treatment has any effect on the result of ulceration surgery. Yet reducing tumor size or necrosis by medical treatment can affect tumor visualization and blur its limits. It is therefore preferable to engage in a multidisciplinary discussion before beginning treatment. Surgery is indicated in various situations [54,55].

In microadenomas [56,57]:

- that resist treatment (rare: approximately 5–10%) or respond only partially with prolactin levels that have not normalized despite high doses of agonists and persisting infertility or irregular menses or amenorrhea,
- where the patient is persistently intolerant to dopamine agonists (low blood pressure, digestive disorders, etc.),
- where the patient chooses to refuse long-term treatment, has a pregnancy project, expresses anxiety over living with a tumor in his/her head or the uncertainty of tumor progression during pregnancy,
- that are mixed secreting microadenomas such as prolactin and GH.

Surgery consists in selective adenomectomy in order to limit the risk of recurrence. Tumors are transspenoidally removed by a sublabial or direct endonasal approach.
No difference in result has been demonstrated between endoscopic or microscopic adenomectomy. In the best surgeons’ hands, 75 to 90% immediate post-operative normalization can be expected, while fertility is restored in over 80% of cases. Transient diabetes insipidus can occur, but it only persists exceptionally. Surgery should be performed by experienced hands, with regular practice of pituitary procedures.

Long term follow up (one year or more) shows that hyperprolactinemia recurs in 15-20% of cases due to infiltration of the anterior pituitary parenchyma or of the dura by tumoral islets.

In macroadenomas:
- that resist treatment (10% of cases) and/or with recurring elevation of prolactin levels. Medical treatment should be resumed once tumor size has been reduced and decompression has been performed,
- with rhinorrhea due to cerebrospinal fluid leaking through a meningeal breach: medical treatment reduces tumor size, uncovering a preexisting breach,
- where diagnosis is uncertain, particularly when tumor size and prolactin levels are dissociated and/or when tumor response to dopaminergic treatment is incomplete. In this case treatment efficiency should not be assessed by prolactin levels but by tumor response,
- where pituitary apoplexy occurs during treatment—an exceptionally rare event— if it is life-threatening.

Extensive macroadenomas are distinct from invasive macroadenomas that colonize every structure they encounter (capsula, cavernous sinus, basis of cranium). Invasive macroadenomas have no chance of being cured surgically while 90% of them respond to dopamine agonist treatment. Therefore medical treatment can even be proposed as a first line treatment to patients with visual disorders. Rapid regression of visual defects needs to be obtained under treatment, and hospitalization may be required to check this at the beginning of treatment.

5.2. Radiotherapy

Its only indications are resistance to medical treatment and when it is too late for surgical decompression. Stereotactic radiotherapy, in particular with a gamma knife, has not been tested in large series or over long periods [58–60].

6. Medical Treatment of Hyperprolactinemia

6.1. Dopamine Agonists

Medical treatment of hyperprolactinemia relies on dopamine agonists [61,62]: bromocriptine (Parlodel®), lisuride (Dopergine®), quinagolide (Norprolac®) [44], cabergoline (Dostinex®) [48]. Objectives in women are to treat hypogonadism and restore normal cycles, but this does not necessarily mean that prolactin levels will become normal. The new drugs now available such as quinagolide and especially cabergoline have become first line treatments over bromocriptine, at least outside of the pregnancy realm, because of their better tolerance and efficiency [1,44,63,64]. The most common secondary effects are digestive (nausea, vomiting). Drowsiness or orthostatic hypotension have also been reported. In cases where macroprolactinomas invade the base of the cranium, rhinorrhea is a real danger during treatment: as the tumor shrinks with medication, any pre-existing breach in the dura mater that was sealed by the tumor might be uncovered, causing a leakage of cerebrospinal fluid [65]. Normal levels of prolactin can be restored within days after treatment is begun but may require months. In men the normalization of prolactin levels also corrects testosterone levels, unless there is an anterior pituitary lesion having destroyed gonadotropic cells.

6.2. Resistance to Dopaminergic Drugs [66]

Approximately 5 to 10% of patients are resistant to any type of dopamine agonists. This is more frequent in men than in women [67], concurring with the fact that prolactinomas are more aggressive in men [41]. A dissociation between antitumor and antisecretory effects can be seen. Surgery can be used in resistant cases to decrease tumor size, after which medical treatment can be resumed if there was any partial response [68,69].

6.3. Long Term Follow Up

Once prolactin levels have normalized, drug dosage or dosage frequency can progressively be decreased in order to maintain normal prolactin levels with the lowest possible drug doses [70,71]. Repeat MRIs are not useful in prolactin-secreting microadenomas where prolactin levels are normal. In macroadenomas, we recommend a control MRI at 3 months with yearly repeats as long as the anti-tumoral effect persists. MRIs can be spaced out thereafter (every 5 years for example).

There is no reported detrimental effect of long-term treatment. But attempts to interrupt medical treatment in microadenomas after long-term treatment have shown that in 30 to 50% of cases, depending on the series, prolactin levels are normal after 5 years, particularly so when microadenomas had disappeared on the MRI. This can also be true, though not so often, of macroprolactinomas, especially when they are no longer visible on the MRI. The longer the treatment was followed, the longer the remanence of normal prolactin after treatment interruption. This implies that “cure” can not be affirmed until several months or even years after treatment interruption [72,73].

6.4. Microadenomas after Menopause

As a general rule, medical treatment of microprolactinomas can be interrupted after menopause [74]. Indeed, hyperprolactinemia may disappear with menopause. In any case, even if prolactin levels remain elevated, their correction does not affect peripheral physiological hypogonadism. And no detri-
mental effect of hyperprolactinemia has ever been clearly demonstrated, including on breast cancer. Hyperprolactinemia does not contra-indicate hormonal substitution in this context [75,76]. In that case there is no need to systematically continue dopaminergic treatment.

6.5. Drug-Induced Hyperprolactinemia

Less often seen with drugs such as “atypical” neuroleptics [77,78], drug-induced hyperprolactinemia is usually caused by psychotropic treatments [79,80]. Dopaminergic agonists are regularly inefficient or even dangerous when used with such drugs, the risk being to increase psychiatric manifestations. When the psychoactive drug can not be interrupted, symptomatic treatment can be proposed after a control MRI, for example substitutive or even contraceptive estrogens or estropogestosterone to correct hypoestrogenism.

7. Conclusion

Hyperprolactinemia is a frequent cause of gonadic disorders both in men and in women. Elevated prolactin levels can have physiological causes, such as pregnancy, or can be due to laboratory artifacts as in “macroprolactinemia”. They can also reveal a hypothalampituitaritary tumor, the most frequent type being prolactinomas. Their management has changed with the occurrence of new treatments, both medical or surgical, the first line treatment being dopaminergic agonists in the vast majority of cases. But management should be tailored to individual cases: we hope that these recommendations based both on scientific literature and medical practice will assist physicians and patients in their choices.

8. French version

A French version of this article is available at doi: 10.1016/j.endo.2007.02.006.

Références