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REVIEW

Differential diagnosis and management of abnormal uterine bleeding due to hyperprolactinemia

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KEYWORDS

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Abstract Abnormal uterine bleeding may be acute or chronic accounting for up to 30% of outpatient visits to gynecologists. Hyperprolactinemia is one of the most common endocrine disorders associated with ovulatory dysfunction that results in menstrual irregularities. Prior to initiating treatment, the various causes (physiologic, pathologic, pharmacologic, or idiopathic) of

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Prolactinoma;
Dopamine agonists

hyperprolactinemia must be elucidated. Prolactin is a stress hormone that increases in response to stressful conditions; therefore, while collecting samples it is necessary to reduce venipuncture stress. A thorough patient history and physical examination will help to identify the cause and to direct therapy. Imaging results must always be assessed along with a patient's clinical history and biochemical parameters when a pituitary tumor is suspected. Magnetic resonance imaging is the method of choice for the diagnosis of microprolactinomas and macroprolactinomas in both initial assessment and follow-up. Several drugs may cause a significant increase in serum prolactin concentration. If clinically feasible, the drug should be discontinued; if this is not possible, it should be substituted with a drug of similar action that does not cause hyperprolactinemia. Prolactinomas are the most common cause of pituitary adenomas affecting women of fertile age leading to significant elevations in prolactin that warrant treatment. Idiopathic hyperprolactinemia may be observed in the presence of elevated serum prolactin levels and in the absence of any other recognized cause of increased prolactin secretion. Dopamine agonists are the mainstay of therapy in prolactinomas and symptomatic idiopathic hyperprolactinemia because they normalize serum prolactin, effectively shrink prolactinomas and normalize gonadal function (i.e. menstruation).

Contents

1. Introduction

Abnormal uterine bleeding (AUB) may be acute or chronic, and is defined as bleeding from the uterine corpus that is abnormal in regularity, volume, frequency, or duration, occurring in the absence of pregnancy (1). Up to 14% of women experience irregular or excessively heavy menstrual bleeding (2). Disorders of the menstrual cycle are a common problem in ambulatory medicine, accounting for up to 30% of outpatient visits to gynecologists (3). A study found that, of 20.1 million visits to physicians, menstrual complaints accounted for 19.1% of the visits (4).

Abnormal uterine bleeding not only puts a heavy economic burden on society (5) but also significantly impacts health-related quality of life (5,6). Although additional research is required, the conservatively estimated annual direct and

indirect economic costs of AUB were approximately $1 billion and $12 billion, respectively. Moreover, these estimates did not include intangible costs and productivity loss due to presenteeism (5).

Menstrual disorders are a common indication for medical visits among women of reproductive age, and heavy menstrual bleeding affects up to 30% of women throughout their reproductive lifetime. These complaints may significantly affect quality of life, result in time-off work, lead to surgical interventions including hysterectomy, and ultimately has a significant impact on the healthcare system (7).

Although most ovulatory disorders elude a defined etiology, many can be traced to endocrinopathies (e.g. polycystic ovary syndrome, hypothyroidism, hyperprolactinemia, mental stress, obesity, anorexia, weight loss, or extreme exercise (i.e., associated with elite athletic training)) (8). The investigation and management of AUB among non-gravid women of reproductive age have been hampered both by confusing and inconsistently applied nomenclature and by the lack of standardized methods for investigation and categorization of the various potential etiologies (8). The International Federation of Gynaecology and Obstetrics has designed the PALM-COEIN system to take into account the myriad causes and entities that contribute to AUB (Table 1) (8). The PALM side of the classification refers to structural causes that could be evaluated and diagnosed on imaging and/or biopsy. The COEIN side allows consideration of underlying medical disturbances that could result in AUB (8).

Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic–pituitary axis in young women and is associated with ovulatory dysfunction that results in menstrual irregularities (9). There is a known relationship between hyperprolactinemia and reproductive disorders, amenorrhea, and irregular bleeding (10). Hyperprolactinemia can occur at any age and the prevalence varies from 0.4% in the normal adult population to as high as 9–17% in women with menstrual problems such as amenorrhea or polycystic ovarian syndrome (9). A study of 1704 women with menstrual-related problems, suggested that hyperprolactinemia is common in patients with menstrual irregularities. Hyperprolactinemia was found to be the cause of AUB (excluding amenorrhea and oligomenorrhea) in 9.4% of patients and secondary amenorrhea in 13.8% of patients from the age of 21–30 years (9). In another analytical descriptive study of 100 women, who were referred to a university hospital for vaginal bleeding without any organic disorder (abnormal pathology of the cervix and vagina, polyp, myoma) or any other cause of AUB (such as thyroid disorders and pregnancy complications), 61% were found to have hyperprolactinemia (10).

Table 1 The FIGO PALM–COEIN classification of abnormal uterine bleeding (8).

Structural (**PALM**)		Non-structural (**COEIN**)
Polyp		**C**oagulopathy
Adenomyosis		**O**vulatory dysfunction
Leiomyoma	Submucosal	**E**ndometriosis
	Other	**I**atrogenic
Malignancy and hyperplasia		**N**ot yet classified

This manuscript will address the differential diagnosis and management of women presenting with AUB due to hyperprolactinemia. The differential diagnosis and management of asymptomatic patients with hyperprolactinemia are not within the scope of this manuscript.

2. Diagnostic approach of a patient with abnormal uterine bleeding due to hyperprolactinemia

2.1. Differential diagnosis

The possible causes of hyperprolactinemia in women presenting with AUB must be elucidated prior to initiating treatment, and these have been summarized in Table 2.

2.1.1. Physiologic causes

When evaluating a patient with AUB due to hyperprolactinemia, the physiologic causes of prolactin elevation including stress, exercise, and sleep should be considered (11). Prolactin is a stress hormone that increases in response to a number of physiologic and stressful conditions including the stress of having blood drawn (12). Studies have shown that coitus produces marked elevation in serum prolactin levels that are sustained for up to 1 h (13,14). Furthermore, sexual intercourse with orgasm induces a well-established immediate prolactin increase of ~300% with an additional prolactin elevation around noon

Table 2 Etiology of hyperprolactinemia (11).

Category	Contributing factor
Physiologic	Coitus, exercise, lactation, pregnancy, sleep, stress
Pathologic	
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
Pharmacologic	Anesthetics, anticonvulsant, antidepressants, antihistamines (H2), antihypertensives, cholinergic agonist, drug-induced hypersecretion, catecholamine depletory, dopamine receptor blockers, dopamine synthesis inhibitor, estrogens: oral contraceptives; oral contraceptive withdrawal, neuroleptics/antipsychotics, neuropeptides, opiates and opiate antagonists

Adapted from (11).

of the next day ($p < 0.05$) (14). During pregnancy, serum prolactin levels increase 10-fold, reaching levels of 150–300 μg/L by term. Moreover, the pituitary gland increases in volume more than 2-fold, primarily due to an estrogen-stimulated increase in the number of lactotrophs (11). Management of women with AUB during pregnancy is out of the scope of this manuscript; however, pregnancy and lactation as a cause of hyperprolactinemia should be excluded prior to initiating therapy.

2.1.2. Pharmacologic causes

The problem of drug-induced hyperprolactinemia is often underestimated, primarily due to the lack of visible symptoms, patients' reluctance to come forward, and/or the clinician's lack of awareness (15). Several medications that may raise serum prolactin above normal are shown in Table 3. Most medications increase serum prolactin either by removing the inhibitor pathways or by directly stimulating prolactin production via the lactotroph cells (15).

2.1.2.1. Antipsychotics. Antipsychotics are the most common cause of pharmacologic hyperprolactinemia (15,16) with galactorrhea and menstrual irregularities reported in over 50% of patients (15). Classification of antipsychotic drugs may be based on their ability to elevate prolactin. Classical antipsychotics are traditionally 'prolactin-raising', whereas the newest class is usually 'prolactin-sparing' (15).

Classical antipsychotics are the most common cause of drug-induced hyperprolactinemia. Plasma prolactin levels have been reported to increase in a dose-dependent manner, but even low daily dosages can cause significant elevations. This increase begins after a few hours and persists during the rest of treatment. The total effect depends on therapy duration, and a medium-term treatment (3–9 weeks) has been found to increase baseline levels up to 10-fold (15).

Table 3 Drugs inducing sustained hyperprolactinemia (15).

Drug class		Generic name
Antipsychotics	Typical	Haloperidol, chlorpromazine, thioridazine, thiothixene
	Atypical	Risperidone, amisulpride, molindone, zotepine
Antidepressants	Tricyclics	Amitriptyline, desipramine, clomipramine, amoxapine
	SSRI	Sertraline, fluoxetine, paroxetine
	MAO-I	Pargyline, clorgyline
Other psychotropics		Buspirone, alprazolam
Prokinetics		Metoclopramide, domperidone
Antihypertensive		Alpha-methyldopa, reserpine, verapamil
Opiates		Morphine
H_2 antagonists		Cimetidine, ranitidine
Other		Fenfluramine, physostigmine, chemotherapeutics

Note: Only drugs with demonstrated ability to induce hyperprolactinemia above the normal range have been included in this table. MAO-I, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitor.
Adapted from (15).

Atypical antipsychotics are characterized by increased antipsychotic efficacy and fewer neurologic and endocrine-related side effects compared with classical antipsychotic drugs. Most of them elicit poor hyperprolactinemic response or no hyperprolactinemia at all (15).

Problems related to hyperprolactinemia occur less often with some atypical antipsychotics than with typical drugs, except with risperidone and amisulpride. Some other atypical antipsychotics, such as clozapine, olanzapine, quetiapine, sertindole, and ziprasidone cause only mild and transient hyperprolactinemia (15).

Risperidone is one of the atypical antipsychotics most likely to induce hyperprolactinemia leading to endocrinologic side effects, such as amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction with a frequency of 1–10% (15).

Amisulpride is a substituted benzamide derivative, characterized by fewer extrapyramidal symptoms but with greater prolactin elevation that is similar to that of conventional antipsychotics, and often clinically relevant. Amisulpride-induced hyperprolactinemia is reported after both acute and chronic treatments and does not seem to be strongly dose-related (15).

2.1.2.2. Antidepressants. The data on the effect of antidepressant drugs on prolactin secretion are limited. Sustained and symptomatic hyperprolactinemia has been demonstrated with the heterocyclic antidepressants such as amitriptyline, desipramine, clomipramine, and amoxapine. However, selective serotonin reuptake inhibitors have been reported to be the most frequent cause of drug-induced hyperprolactinemia. Among those, sertraline appears to be the most frequent cause of sustained hyperprolactinemia, and fluoxetine and paroxetine may also induce pathologic and symptomatic increases in prolactin levels. Most of the other antidepressants do not induce hyperprolactinemia or induce only transient or within normal range variations with little clinical relevance (15).

2.1.2.3. Others. Two prokinetic drugs, commonly used in gastrointestinal disorders, induce hyperprolactinemia via a dopamine–antagonistic mechanism. Metoclopramide, a prokinetic drug used in nausea, vomiting, diabetic gastric stasis, and gastroesophageal reflux, is a potent stimulator of prolactin release. Domperidone is used for gastrointestinal motility disorders and for the prevention of gastrointestinal symptoms associated with dopaminergic treatment of Parkinson's disease. A long list of other compounds raise prolactin levels to varied degrees, including antihypertensive, opiates, H2 antagonists, estrogens, anti-androgens, anticonvulsants, and cholinomimetics. Hyperprolactinemia has also been documented after autologous blood stem-cell transplantation and during chemotherapy, even though disturbances of prolactin seem to occur less frequently than impairments of the hypothala mus–pituitary–gonad/thyroid axis after intensive treatment and blood marrow transplantation (15).

2.1.3. Pathologic causes

Pituitary stalk damage: patients with large non-functioning pituitary tumors, craniopharyngiomas, or granulomatous infiltration of the hypothalamus can develop hyperprolactinemia because of pituitary stalk compression or dopaminergic neuronal damage (Fig. 2) (11). Prolactinomas are the most

common pituitary tumor (~50%) (17) and usually appear in women aged 20–50 years (17,18). It is reported that more than 90% of prolactinomas are microprolactinomas (< 1.0 cm in diameter), whereas the rest are macroprolactinomas (≥ 1.0 cm) (17). A study of 1704 women with menstrual-related problems revealed that 47.5% of patients with secondary amenorrhea and 4.5% of patients with AUB (excluding amenorrhea and oligomenorrhea) from the age group 21–30 years had hyperprolactinemia due to prolactinomas (19). Aside from high prolactin levels during pregnancy and lactation, prolactinoma is the most frequent cause of persistent hyperprolactinemia (19).

Systemic disorders: patients with renal insufficiency may have moderate hyperprolactinemia caused by impaired renal degradation of prolactin and altered central prolactin regulation. About 30% of patients with chronic renal failure (11,20) and up to 80% of patients on hemodialysis (20) have raised prolactin levels. Hyperprolactinemia develops due to either decreased clearance or increased production of prolactin as a result of disordered hypothalamic regulation of prolactin secretion (11,20). Correction of renal failure by transplantation results in normal prolactin levels (20).

Some patients with primary hypothyroidism have moderate hyperprolactinemia. Long-term or inadequately treated primary hypothyroidism can cause pituitary hyperplasia that may mimic a pituitary tumor (11). Around 40% of patients with primary hypothyroidism have mild elevation of prolactin levels that can be normalized by thyroid hormone replacement (20).

2.1.4. Idiopathic hyperprolactinemia

Idiopathic hyperprolactinemia can be defined as the presence of elevated serum prolactin levels in a patient in the absence of demonstrable pituitary or central nervous system disease, and in the absence of any other recognized cause of increased prolactin secretion (21). It is often secondary to a small microprolactinoma not identified by MRI (22). Spontaneous normalization of prolactin levels has been found to occur in approximately 30% of patients with idiopathic hyperprolactinemia (11).

2.2. Stepwise diagnostic approach

2.2.1. Patient history and physical examination

A complete history and physical examination will help direct the need for further investigation and treatment. Exploring the signs and symptoms in the past and at presentation will help the clinician to identify the possible cause of high serum prolactin levels (Table 2). A complete medication history must be collected because some medications are known to elevate prolactin levels (Table 3).

2.2.2. Serum prolactin testing and interpretation

If serum prolactin results appear to be compromised, testing must be repeated, if possible, during the early follicular phase of the menstrual cycle at 15–20 min intervals (2–3 samples) to account for possible prolactin pulsatility (11). While collecting samples for serum prolactin assessment, it is necessary to reduce venipuncture stress (11), as the stress of having blood drawn may cause a marked elevation in serum prolactin (12).

Samples should ideally be collected:

- During the early follicular phase of the menstrual cycle.
- Mid-morning or at least 1 h after waking up.
- Once the patient has rested for at least 20 min after arriving at the clinic/laboratory.

Refer to Table 4 for interpreting serum prolactin levels.

2.2.2.1. Serum prolactin reference intervals and reliability of immunoassay platforms. Reliable measurement of sex hormones (such as prolactin) is indispensable in the evaluation of the hypothalamo–pituitary–gonadal axis (24). Although mass spectrometry is the gold-standard for evaluation, it is often limited to a few reference laboratories (24). Platform immunoassays are rapid, automatable, and easy to perform; however, their specificity, sensitivity, and precision are questionable (24,25). The parametric prolactin reference intervals given by the manufacturers for females were found to be considerably higher for Centaur (78%), AIA (42%), Architect (41%), Access (39%), and Immulite (34%), suggesting a subtle

Table 4 Interpreting serum prolactin levels.

Serum prolactin (μg/L)	Interpretation
< 25	Normal (11)
> 25 but < 100	1. Two successive measurements of serum prolactin above normal are defined as hyperprolactinemia (23). Considering that the patient presented with the symptoms of menstrual irregularity, suspect the presence of microprolactinoma after re-evaluating the physiologic causes. Repeat serum prolactin testing during the early follicular phase. If prolactin continues to remain elevated, recommend imaging tests. 2. Suspect hyperprolactinemia due to stalk effect caused by a large non-prolactin secreting adenoma (22). It is crucial to conduct imaging tests to rule out the stalk effect in such cases. 3. Check for the Hook effect. When serum prolactin levels are not as high as expected, especially in the presence of a macroprolactinoma, the assay should be repeated after a 1:100 serum sample dilution to overcome a potential hook effect (11). If imaging tests are clear, dilution test is negative for the Hook Effect, and other etiologies of hyperprolactinemia have been ruled out, suspect a small microprolactinoma not visible on imaging and start treatment.
> 250	Diagnostic for the presence of prolactinoma (11)
> 500	Diagnostic for macroprolactinoma (≥ 10 mm in diameter) (11)

Note: selected drugs, including risperidone and metoclopramide, may raise serum prolactin above 200 μg/L without evidence of adenoma (11).
Unit conversion: 1 μg/L (ng/mL) = 43.5 pmol/L = 0.0435 nmol/L = 21.2 mIU/L.

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difference in immunoassay antibody specificity, emphasizing the difficulty in establishing common reference intervals for immunoassays (25). Results provided by various laboratories are therefore difficult to compare limiting their usability (24).

Intervals for prolactin were found to be significantly influenced by hormonal status (Fig. 1), with upper limit of luteal phase higher than follicular phase, and upper limits of both phases higher than those in postmenopausal women. Also, the upper limit of prolactin in the luteal phase exceeded the combined reference intervals by 4.1% for both Advia Centaur and the Immulite 2000XP platforms, which supports grouping women based on the menstrual cycle (24). This emphasizes the need for clear selection criteria when assembling populations for establishing endocrine reference intervals (24).

If assay results appear to be compromised, testing must be repeated, preferably during the early follicular phase of the menstrual cycle, as recommended (11).

2.2.3. Imaging tests

Imaging results must always be assessed along with a patient's clinical history and biochemical parameters when a pituitary tumor is suspected (26).

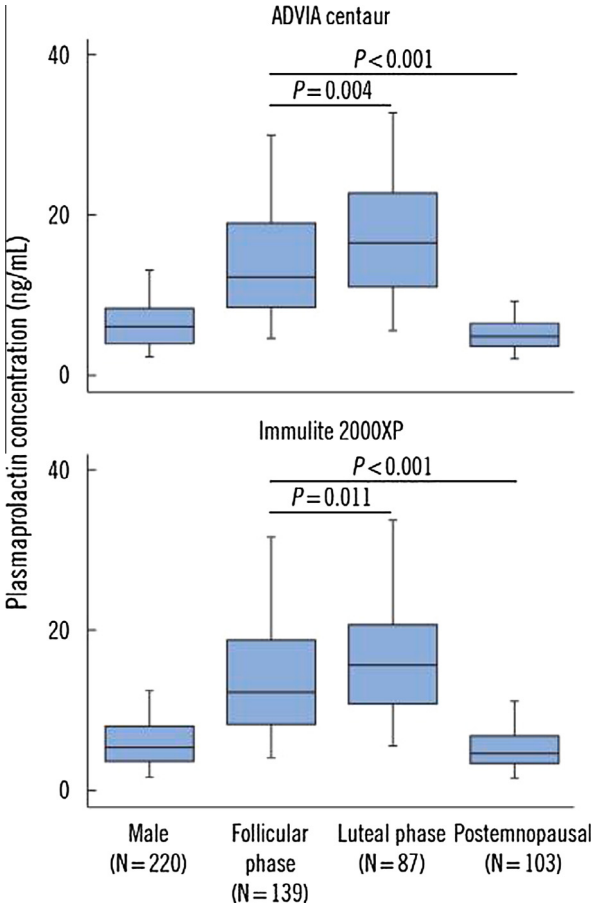

Figure 1 Box–Whisker plots showing the distribution of prolactin values as measured with the Advia Centaur or Immulite 2000XP platforms. Middle lines represent medians. The central box represents the values from the lower to upper quartile. Adapted from (24).

Magnetic resonance imaging (MRI) is the method of choice for the diagnosis of microprolactinomas (26) and macroprolactinomas (17) in both initial assessment and follow-up (Fig. 2). MRI is the examination of choice for sellar and parasellar pathologies due to its superior soft tissue contrast, multiplanar capability, and lack of ionizing radiation (27). It provides not only information on the size of the tumor, but also on the relationship with the adjacent anatomic structures and neuro-ophthalmologic pathways (17,27). MRI is also useful for follow-up of patients with macroprolactinomas who are treated with dopamine agonist's because it shows the reduction of tumor size as well as other alterations that can be associated with chronic medical treatments such as intratumoral hemorrhage, intrasellar chiasma and optic nerves invagination, and empty sella (17,18). MRI is preferred to computed tomography (CT) due to its superior definition of very small lesions in the pituitary sella and anatomic definition prior to surgery (28).

Computed tomography, although less frequently used for evaluating sellar and parasellar lesions, is a useful tool that depicts soft tissue calcification, bony destruction, and surgically relevant bony anatomy (27). It is valuable, particularly when MRI is contraindicated (i.e. in patients with pacemakers or metallic implants in the brain or eyes) (27). However, the two important drawbacks that limit its use for evaluating pituitary lesions are less optimal soft tissue contrast and radiation exposure (27). They may be used as an alternative diagnostic tool to rule out a pituitary macroadenoma associated with stalk effect (29).

3. Management of abnormal uterine bleeding due to hyperprolactinemia

It is important that the pathologic relevance of hyperprolactinemia is established before commencing treatment (11,20).

3.1. Medication-induced hyperprolactinemia

Several drugs may cause a significant increase in serum prolactin concentration that is frequently associated with symptoms (15).

Medications that can cause hyperprolactinemia should be discontinued for 48–72 h, if safe to do so, and serum prolactin testing should be repeated. Sometimes the causative agent is essential for the patient's health (e.g., a psychotropic agent), but it may cause symptomatic hypogonadism. In these patients, treatment with a dopamine agonist should be avoided because it might compromise the effectiveness of the psychotropic drug and the patient should simply be treated with a replacement of sex steroids (20).

The drug is discontinued if clinically feasible; if this is not possible, a drug with a similar action that does not cause hyperprolactinemia should be substituted. If this is not feasible, the treating physician should consider the cautious administration of a dopamine agonist in consultation with the patient's physician (11).

It is important to ensure that hyperprolactinemia in an individual patient is due to medication and is not due to a structural lesion in the hypothalamic/pituitary area. This can be accomplished by (1) stopping the medication temporarily to determine whether prolactin levels return to normal, (2) switching to a medication that does not cause hyperprolactinemia (in

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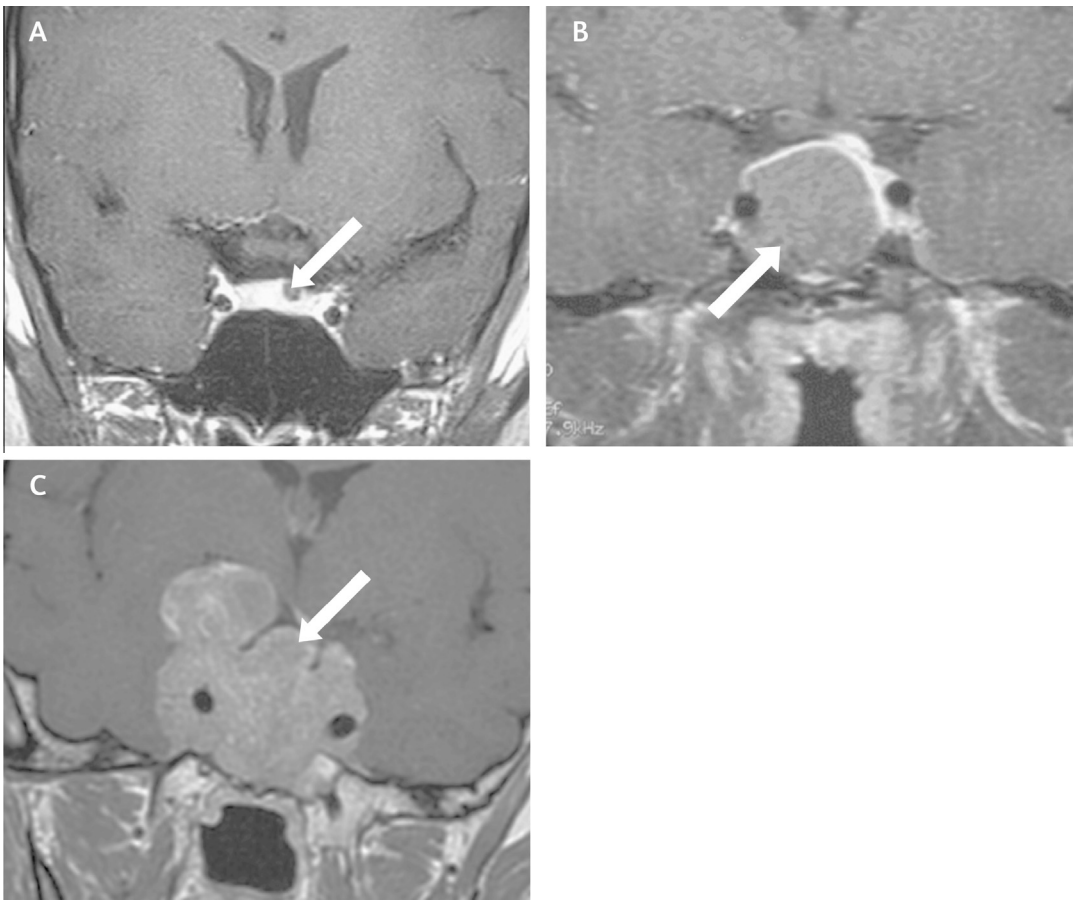

Figure 2 T1-weighted post-contrast MRI scans of (A) pituitary microprolactinoma to the left of midline; (B) non-functional pituitary macroadenoma associated with stalk effect (the pituitary stalk is deviated to the left side with compression and displacement of normal pituitary gland superiorly and to the left); (C) coronal view of a giant macroprolactinoma with extrasellar extension.

consultation with the patient's psychiatrist for psychoactive medications), or (3) performing an MRI or CT scan of the hypothalamic/pituitary area (16).

The management of antipsychotic-induced hyperprolactinemia should aim to minimize the side effects, thus optimizing therapy compliance and reducing the risk of subsequent psychotic relapses. Avoiding hyperprolactinemia and its long-term complication means improving treatment outcomes and enhancing quality of life (15). The discontinuation of neuroleptic therapy or addition of dopamine agonists may worsen the psychosis. The reduction of the neuroleptic dose may not necessarily lead to a decrease in prolactin; hence, switching to prolactin-sparing agents acquires great relevance (15).

Although dopamine agonists have successfully been used in patients with antipsychotic-induced hyperprolactinemia, bromocriptine treatment is reported to be associated with exacerbation of an acute psychotic state in psychotic women (15). Treating patients who have antipsychotic-induced hyperprolactinemia with dopamine agonist therapy is controversial; studies have shown that dopamine agonist therapy will normalize prolactin levels in only up to 75% of patients, but may exacerbate the underlying psychosis. Discontinuation or substitution of an antipsychotic agent should not be undertaken without consulting the patient's physician (11).

3.2. Idiopathic hyperprolactinemia

Dopamine agonists effectively treat patients with prolactinomas and symptomatic idiopathic hyperprolactinemia (30,31). Cabergoline effectively normalized serum prolactin levels and restored gonadal function in patients with microprolactinoma or idiopathic hyperprolactinemia (31). In a retrospective analysis of 455 patients with hyperprolactinemia (41% microadenoma; 42% macroadenoma; 16% idiopathic hyperprolactinemia; 1% empty sella), cabergoline normalized prolactin in 92% of patients with idiopathic hyperprolactinemia and microprolactinoma ($n = 244$) and 77% of patients with macroprolactinoma ($n = 181$) (32). Cabergoline also normalized prolactin in 84% of patients intolerant to, and 70% of patients resistant to, bromocriptine. Additionally, patients with idiopathic hyperprolactinemia or microprolactinoma required a lower median dose of cabergoline to obtain prolactin normalization, compared with those with macroprolactinoma (32). A meta-analysis compared the effectiveness of cabergoline and bromocriptine in treating patients with idiopathic hyperprolactinemia and prolactinomas (33). The results favored the use of cabergoline in the treatment of idiopathic hyperprolactinemia and prolactinomas, normalizing serum prolactin and menstruation with a relative risk of 0.67 [95% CI 0.57, 0.80] versus bromocriptine with a relative risk of

0.74 [95% CI 0.67, 0.83] (33). Stable normoprolactinemia was also effectively maintained with short-term maintenance therapy of cabergoline 0.5 mg twice per week in 164 *de novo* patients with idiopathic hyperprolactinemia or microprolactinoma (34).

A meta-analysis of 19 studies (743 patients) aimed to assess the effect of dopamine agonist withdrawal in idiopathic hyperprolactinemia and prolactinomas (35). Dopamine agonist withdrawal was associated with persistent normoprolactinemia in 21% of the overall patient population. By stratified analysis, persistent normoprolactinemia was higher in patients with idiopathic hyperprolactinemia (32%) compared with those with microprolactinoma (21%) and macroprolactinoma (16%). Furthermore, treatment with cabergoline for more than 2 years was associated with the best outcome (35).

3.3. Prolactinomas

Prolactinomas are the most common pituitary adenomas that affect young women at a fertile age (18,36). Hyperprolactinemia causes hypogonadism, menstrual irregularities or amenorrhea, infertility and sexual dysfunction in women (18,36), adversely impacting overall quality of life (37). Most prolactinomas are microadenomas and rarely increase in size over time. Studies examining the natural history of untreated microprolactinomas have shown that significant growth of these tumors is uncommon (18). A microadenoma with documented evidence of growth demands therapy because 7% may grow into macroadenomas (18). Patients with suspected microprolactinoma should be treated because it increases the risk of short-term tumor growth by 10% and premature osteoporosis during sustained hyperprolactinemia (38). Fractures are also more common in patients with untreated hyperprolactinemia compared with patients treated with cabergoline (39). The presence of a macroadenoma raises the probability for the tumor in question to have biologic characteristics that confer a propensity to grow (36). Macroprolactinomas may cause headache, visual disturbance, and hypopituitarism (36,40). It is also associated with significant prolactin elevations producing symptoms that warrant treatment (18,40). Additionally, dopamine agonist therapy restores gonadal function and increases vertebral bone mineral density in most hyperprolactinemic women (39).

3.3.1. Dopamine agonists

Medical therapy with dopamine agonists is the initial treatment of choice in all prolactinomas (18,40–43) because it is found to be efficacious in 80–90% of patients with prolactinomas (44). Dopamine agonists inhibit prolactin secretion, reduce tumor volume (40,41,45), and restore gonadal function in women with prolactin-secreting micro- or macroadenomas (11,46). The most commonly used dopamine agonists are the ergot-derived dopamine agonist's, bromocriptine and cabergoline, and the non-ergot-derived dopamine agonist, quinagolide (41).

Bromocriptine was introduced decades ago as the first medical treatment for prolactinomas (18,41). It has a short elimination half-life and dosage range from 2.5 mg to 15 mg and is given up to three-times daily (18,41). It normalizes prolactin, restores gonadal function, and induces tumor shrinkage in 60–80% of patients with microprolactinomas and 50–70% of patients with macroprolactinomas (41). Side effects due to bromocriptine are the main reason for treatment interruption in 12% of patients (18,41).

Cabergoline is the preferred dopamine agonist in the treatment of prolactinomas (36,41,42,47). It is a potent D2 dopamine receptor agonist (41,47) with a mean starting dose of 0.25–0.5 mg twice weekly (41). The average dose for microprolactinomas is 0.5 mg/week and for macroprolactinomas is 1 mg/week (41). Several studies have demonstrated the efficacy of cabergoline in normalizing prolactin concentrations and in inducing tumor shrinkage, especially in microprolactinomas (41). It normalizes prolactin in 75–90% of patients with micro- or macroprolactinomas with an average decrease in tumor volume of 72–92% (41). It has also been proven to be effective in patients with resistance to other dopamine agonists including bromocriptine (41,47), and induces fewer and less severe side effects (18,41) because the rate of discontinuation is only 4% (41). Cabergoline administered long-term at low-doses (0.5–3 mg once or twice a week) decreased tumor volume by >80% in 61% of patients with macroprolactinoma at 12–24 months follow-up ($p < 0.001$), with a significant reduction of 41% reported as early as 3 months after treatment ($p < 0.001$) (31). In a larger study including 110 patients, macroprolactinemia shrinkage of >80% was observed in 92.3%, with disappearance of tumor mass in 61.5% of naïve patients treated with cabergoline at standard doses for 12–36 months. Furthermore, tumor shrinkage and/or disappearance were observed in patients intolerant or resistant to bromocriptine and quinagolide, but to a lesser degree (48). Hyperprolactinemia is often associated with metabolic and hormonal complications (49). Cabergoline is superior to bromocriptine when it comes to affecting atherogenic dyslipidemia, insulin sensitivity, and circulating levels of cardiovascular risk factors in hyperprolactinemic patients; therefore, cabergoline is the preferred treatment (49).

Some patients may remain in long-term remission after a period of several years of dopamine agonist treatment; however, there are no signs to predict whether drug discontinuation will be successful (50). A recent report indicated that dopamine agonists can be safely withdrawn in patients with long-term normalization of prolactin levels and with no evidence of tumor on MRI (50). Successful discontinuation of cabergoline treatment has been reported in 31–75% of patients with prolactinomas treated for at least 2 years (51).

A trial of tapering and discontinuation of dopamine agonists may be initiated if a patient has normal prolactin levels for at least 2 years (Endocrine Society Guidelines) or 3 years (Pituitary Society Guidelines) with a marked reduction in tumor volume (11,50). Close monitoring during dose tapering and after discontinuation to detect recurrence of hyperprolactinemia and tumor enlargement is required so that treatment can be promptly resumed (11,50,51). The 5-year Kaplan–Meier estimate of recurrence after cabergoline withdrawal was low in patients achieving tumor disappearance and did not differ in non-tumoral hyperprolactinemia (24%), microprolactinomas (26.2%), and macroprolactinomas (32.6%) (52). Recurrence of hyperprolactinemia was higher in patients still presenting small remnant tumors on MRI (41.5% in micro- and 77.5% in macroprolactinomas) (52). In cases of hyperprolactinemia recurrence, tumors did not regrow nor did any symptoms reappear (52). Endocrine Society Clinical Practice Guideline suggests 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 years, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI" (11).

3.3.2. Dopamine agonist non-responders

According to the Endocrine Society Guidelines, the dosage of dopamine agonists should be increased to the maximum tolerable dose in patients who do not achieve normal prolactin levels or who do not show significant decrease in tumor size (11). Patients resistant to bromocriptine should be switched to cabergoline (11). Studies have reported that 85% of bromocriptine-resistant subjects respond to cabergoline or quinagolide with a decrease in prolactin levels (53,54). Cabergoline normalized serum prolactin, induced tumor shrinkage, and improved clinical symptoms in patients with micro- and macro-prolactinoma resistant to bromocriptine and/or quinagolide (31,54). Patients unable to tolerate cabergoline or who were not responsive to dopamine agonists should be referred for trans-sphenoidal surgery (11). In patients unsuccessful with surgical treatment or those with invasive malignant prolactinomas, radiation therapy should be considered (11).

3.3.3. Trans-sphenoidal surgery

Medical treatment may be partially or completely ineffective in about 20% of patients with prolactinomas; in these cases, surgery may be indicated (trans-sphenoidal route) (36). Treatment ineffectiveness is mainly due to intolerance and/or resistance to dopamine agonist therapy. The success of trans-sphenoidal surgery is based on the size of the tumor and highly dependent upon the experience of the neurosurgeon. Surgery has been reported to restore prolactin concentration in 85–90% of patients with microprolactinomas and 18–80% of patients with macroprolactinomas. In patients with macroprolactinomas with parasellar extension, trans-sphenoidal surgery alone is not curative. Furthermore, trans-sphenoidal surgery may lead to hypopituitarism. Hypopituitarism is more common after surgery in patients with macroprolactinomas than microprolactinomas. The overall mortality with trans-sphenoidal surgery is less than 0.5% (41).

3.3.4. Radiotherapy

Radiotherapy is indicated only in the control of tumor growth in invasive or aggressive cases (36). It is usually applied after unsuccessful trans-sphenoidal surgery (18,41). In a series of patients with unsuccessful trans-sphenoidal surgery, conventional, fractioned radiotherapy normalized prolactin concentrations in approximately 34% of patients. Moreover, the cumulative risk of hypopituitarism after postoperative radiotherapy is approximately 50% at 10–20 years (41).

3.3.5. Suspected pregnancy

By definition, pregnancy should be excluded in differential diagnosis of AUB. However, pregnancy may occur during the course of treatment. In general, dopamine agonist therapy should be discontinued in women as soon as pregnancy is suspected. Dopamine agonist therapy may be continued in women with macroadenomas (especially invasive tumors) who become pregnant while on therapy and those who have not undergone prior surgery or radiation therapy. It is not recommended to perform serum prolactin measurement during pregnancy because there is a significant physiologic rise in prolactin (11). It is also not recommended to conduct imaging tests unless tumor growth is suspected, evidenced by visual field compromise (11,55,56).

3.4. Normalization of menstruation with dopamine agonist

Hyperprolactinemia decreases the pulsatile secretion of gonadotrophin-releasing hormone impairing the release of luteinizing hormone and follicular-stimulating hormone. Excess prolactin directly influences the steroid–genetic activity of the ovary causing menstrual irregularities (57). Dopamine agonists not only effectively normalize prolactin levels and shrink prolactinomas, but also normalize menstruation (11). Ovulation rates achieved with dopamine agonist therapy alone are around 80–90% if hyperprolactinemia is the only cause for anovulation (18,20). Bromocriptine, given continuously, reduces prolactin which leads to resumption of menstruation and ovulation within 4–8 weeks of therapy (20). In a study of 183 infertile women with hyperprolactinemia, the rates of irregular menstruation ($p = 0.011$) and galactorrhoea ($p < 0.001$) were significantly lower in patients treated with cabergoline than when treated with bromocriptine (58). Additionally, significantly more women given cabergoline (82%) got pregnant than those on bromocriptine (56.4%; $p < 0.001$) (58). In another study conducted in 124 hyperprolactinemic women, cabergoline resumed menses in 52 women with amenorrhea with presumptive evidence of ovulation in 49 women (59). A randomized crossover trial of 20 patients with hyperprolactinemia given quinagolide or cabergoline for 12 weeks reported normoprolactinemia in 90% on cabergoline and in 75% on quinagolide. Both groups showed similar improvements in amenorrhea, oligomenorrhea, galactorrhoea, and impotence (30). A meta-analysis of normalization of serum prolactin levels and menstruation with return of ovulatory cycle also favored treatment with cabergoline (33). The effect of dopamine agonist therapy in normalizing different patterns of menstrual irregularities caused by hyperprolactinemia may be an interesting subject for future clinical studies.

3.5. Macroprolactinemia

Macroprolactin is less bioactive, and macroprolactinemia should be suspected when typical symptoms of hyperprolactinemia are absent (11). Studies of patients with hyperprolactinemia have revealed that up to 40% have macroprolactinemia (11,60). Macroprolactin may also account for a significant proportion of idiopathic hyperprolactinemia cases (61). Macroprolactin is an antigen–antibody complex of higher molecular mass than prolactin (>150 kDa), consisting of monomeric prolactin and immunoglobulin G (11,60,61). The term 'macroprolactinemia' is used when the concentration of macroprolactin exceeds 60% of the total serum prolactin concentration determined by polyethylene glycol precipitation (60). Macroprolactin not only interferes with prolactin assays (62) but also is undetectable in many commercial assays (11). Because macroprolactinemia is a common cause of hyperprolactinemia, screening may eliminate unnecessary investigation and inappropriate treatment (11,62,63).

4. Conclusions

Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic–pituitary axis in young women, and is associated with ovulatory dysfunction that results in menstrual irregularities (9). In women presenting with AUB and high levels of serum prolactin, the possible causes of hyperprolactinemia (physiologic, pathologic, pharmacologic, or idiopathic) must be elucidated prior to initiating treatment. A thorough history and physical examination will help direct the need for further investigation and treatment.

It is important that the pathologic relevance of hyperprolactinemia is established before commencing treatment (20). Antipsychotics are the most common cause of pharmacologic hyperprolactinemia. The extent of prolactin increase is not only dependent on drug characteristics (i.e., class of antipsychotic and dose administered), but also on patient's sex and age (15). Dopamine agonists normalize serum prolactin in symptomatic idiopathic patients (30), effectively shrink prolactinomas (11), and normalize menstruation (11). For prolactinomas, clinical treatment with dopamine agonists is the gold standard, with cabergoline as the first choice (36,42) due to its higher efficacy in normalizing prolactin levels, increased rate of pituitary tumor shrinkage (11), and superior tolerability (36). Dose tapering and discontinuation may be initiated in patients with normal prolactin levels for at least 2 years (11) or 3 years (50), with a marked reduction in tumor volume with close monitoring (11,50). Endocrine Society Clinical Practice Guidelines suggests 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 years, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI" (11). The efficacy of cabergoline has limited the indication for surgery. Trans-sphenoidal surgery is reserved for patients with intolerance and/or resistance to dopamine agonists. Multimodal therapy containing pretreatment with dopamine agonists, surgical debulking, and subsequent adjuvant radiotherapy may be necessary for giant or invasive prolactinomas (36,41).

Contribution to authorship

All authors were involved in the conception of the manuscript, literature review, meeting attendance, drafting, and reviewing the manuscript.

Conflict of interest

Abdallah Adra, Mazen Yousef El Zibdeh, Abdul Malek Mohammed Abdul Malek, Amir H. Hamrahian, Amr Mohamed Salaheldin Abdelhamid, Annamaria Colao, Elie Anastasiades, Essam Moustafa Aboul Fetooh Ahmed, Jihad Ibrahim Ezzeddine, Mahmoud Ibrahim Abd El Sattar, Suleiman Tawfiq Dabit, Wadih Ghanameh, and Faysal El-Kak have no competing interests. Navid Nedjatian is an employee of Pfizer Gulf and Levant States.

Details of ethics approval

An ethics committee review was not required as no studies or trials involving human or animal subjects, or medical records were conducted for this manuscript.

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