Physiopathology, Diagnosis, and Treatment of Hyperprolactinemia

14

Valentina Gasco and Silvia Grottoli

Contents

V. Gasco · S. Grottoli (✉)
Department of Medical Science, Division of Endocrinology, Diabetes and Metabolism, Turin, Italy
e-mail: valentina.gasco@unito.it; ninagro@yahoo.it

F. F. Casanueva, E. Ghigo (eds.), *Hypothalamic-Pituitary Diseases*, Endocrinology,
https://doi.org/10.1007/978-3-319-44444-4_15

Abstract

Prolactin is a pituitary hormone that plays a pivotal role in a variety of reproductive functions. Hyperprolactinemia is a common condition that can result from a number of causes, including medication use and hypothyroidism as well as pituitary disorders. Depending on the cause and consequences of the hyperprolactinemia, selected patients require treatment. The underlying cause, sex, age, and reproductive status must be considered.

Keywords

Prolactin · Hyperprolactinemia · Treatment · Dopamine agonist · Pregnancy · Resistance · Cure

Introduction

Hyperprolactinemia (HPRL) is a common condition that can result from a number of causes, including medication use and hypothyroidism as well as pituitary disorders.

Indeed, HPRL is the more frequent pituitary dysfunction in clinical practice, and it is an important marker of hypothalamic-pituitary disease.

Regardless of etiology, HPRL may result in hypogonadism, infertility, and galactorrhea, or it may remain asymptomatic. Bone loss occurs secondary to HPRL-mediated sex steroid attenuation.

This chapter, after a brief recall on regulation of prolactin (PRL) secretion and its physiology, reviews the causes of HPRL, the diagnostic workup, and the treatment options and, finally, analyzes some treatment pitfalls.

Regulation of Prolactin Secretion

Human PRL is a 199-amino acid polypeptide of 23 kDa of molecular weight, similar in structure to growth hormone (GH) (Melmed and Kleinberg 2003). Its gene is located on chromosome 6. PRL, GH, and placental lactogen share a similar structure because they derive from a common ancestral gene.

PRL is secreted by the anterior pituitary gland by two populations of cells, lactotroph cells, which represent 15–25% of the anterior pituitary cells and secrete only PRL, and mammosomatotroph cells, a minor cell population, which co-secrete PRL and GH. Like most anterior pituitary hormones, PRL is under dual regulation

by hypothalamic hormones delivered through the hypothalamic-pituitary portal circulation: the balance between the two types of signals determines the amount of PRL released from the anterior pituitary gland. Under most conditions the predominant signal is inhibitory, preventing PRL release, and is mediated by the neurotransmitter dopamine (DA). The tuberoinfundibular dopamine (TIDA) neurons of the arcuate nucleus in the hypothalamus release DA into the portal pituitary circulation; DA is delivered via the pituitary stalk to the lactotroph cells, and here, acting via D2 receptors, DA inhibits PRL gene expression and secretion, increasing potassium conductance and thereby hyperpolarizing the cell membrane. Any mechanism that might interfere with the delivery or action of DA will increase serum PRL levels. However, DA is not the only PRL inhibitory factor. In fact, several molecules, including endothelin-1, transforming growth factor-β1, and calcitonin, which act in an endocrine or paracrine fashion, have been identified.

PRL is also regulated by stimulating agents. Among them, serotonin, thyrotropin-releasing hormone (TRH), basic fibroblast growth factor, epidermal growth factor, vasoactive intestinal peptide (VIP) (Kato et al. 1984), oxytocin, and opiates should be mentioned. Estrogens are important regulators of PRL production, enhancing growth of PRL-producing cells and stimulating PRL production directly, as well as inhibiting DA (Cookson 1981).

Beside the pituitary, 20% of PRL concentration relies on extrapituitary production. Extrapituitary PRL is produced by several tissues, such as the brain, mammary epithelial cells and tumors, endometrium, myometrium, lacrimal and sweat glands, skin fibroblasts, and lymphoid organs and cells (Ben-Jonathan et al. 1996).

Prolactin Physiology

Normal PRL levels are considered to be lower than 25 ng/ml for females and 20 ng/ml for males (1 ng/ml is equivalent to 21.2 mUI/l).

PRL is secreted in a pulsatile manner, following a circadian rhythm (Freeman et al. 2000; Rickenlund et al. 2004). PRL levels peak during REM sleep and in the early morning: maximum PRL level is reached 4 h after sleep onset, while the minimum level occurs 6 h after waking up (Frantz 1978).

The PRL receptor is a member of the type 1 cytokine receptor family (Cosman et al. 1990). PRL receptor is a single-pass transmembrane chain that is encoded by its gene on chromosome 5. The PRL receptor gene is comprised of at least ten coding exons. Multiple transcripts, reflecting alternative splicing variants and transcription start sites, account for some of the variability in PRL receptor structure and tissue distribution (Bole-Feysot et al. 1998). This mechanism provides three different isoforms that differ in the length of the cytoplasmic domain (short, intermediate, and long PRL receptor) (Goffin and Kelly 1997; Kelly et al. 1991). In addition, a soluble form, identical to the extracellular domain of the transmembrane PRL receptor, has been identified (Amit et al. 1997; Fuh and Wells 1995; Postel-Vinay et al. 1991).

PRL binds to its receptor through a binding site, forming an inactive complex, which allows for the interaction of a second PRL binding site to another PRL receptor (Goffin

and Kelly 1997; Goffin et al. 1996). The formation of 1:2 complexes of the hormone with its receptor is the essential first step in the transmission of the biologic signal within target cells. Several signaling pathways are activated by the PRL-PRL receptor interaction, but the most important is the phosphorylation of JAK/STAT molecules that leads to gene transcription. Upon ligand-induced dimerization of PRL receptors, JAK2 phosphorylates specific tyrosine residues on the receptor intracellular domain and autophosphorylates residues within the kinase. These phosphotyrosines serve as docking sites for the signal transducer and activator of transcription (STAT) protein, which then translocates to the cell nucleus and activates target genes.

The actions of the kinase are counteracted by multiple tyrosine phosphatases, which rapidly dephosphorylate specific proteins, and maintain the steady-state level of tyrosine phosphorylation at a very low level in the absence of hormonal stimulation (Berchtold et al. 1998).

In addition to the STAT-dependent events triggered by JAK2 activation, there are other STAT-independent signaling pathways that can be activated when PRL binds to its receptor. Src-family kinases may be involved in PRL signaling by virtue of their ability to couple to multiple signaling intermediates. Phosphatidylinositol-3'-kinase, mitogen-activated protein kinases (MAPKs), and protein kinase C have each been observed to be activated by PRL in some systems (Bole-Feysot et al. 1998). STAT-independent pathways have been proposed for PRL signaling, but the physiologic relevance of such mechanisms is not yet clear. It has been suggested that STAT-independent signaling mediates the mitogenic actions of PRL (Das and Vonderhaar 1997).

The best known role of PRL in humans is the development and stimulation of mammary glands during pregnancy to produce milk (lactogenesis). Plasma levels are raised after childbirth and during breastfeeding, and PRL suppresses gonadotrophins in the postpartum period, a contraceptive effect. Although in the pituitary PRL is present in equal amounts in males and females, its physiological role, well established for female reproduction, is still obscure for the male counterpart.

In addition, PRL plays a role in other functions tightly linked to maternity, as suggested by the observation that in mice with altered expression of PRL receptor, ovulation is impaired (Bole-Feysot et al. 1998) and induction of maternal behavior is compromised (Feldman et al. 1993). Recently, this role of PRL in parental behavior has been suggested also in men (Gettler et al. 2012).

Moreover, PRL receptor expression has been demonstrated not only in the breast but also in different cells and tissues, such as the brain, endometrium, ovary, testicle, prostate, pancreas, liver, kidney, intestine, skin, lung, myocardium, lymphoid cells, adipocytes, and endothelial cells (Ignacak et al. 2012; Melmed et al. 2011). Likewise, paracrine-type local PRL secretion (not DA dependent) is known to exist in some of these tissues.

Apart from the effects on other hormones of pituitary- gonadal axis, numerous other various biological functions of PRL have been identified in many aspects of physiological and metabolic processes. In mammals, it stimulates phospholipid synthesis in the alveolar cells of the fetal lung (Hamosh and Hamosh 1977) and also stimulates lipoprotein lipase activity in hepatocytes (Machida et al. 1990). It increases bile secretion as well (Lin et al. 1992). The direct action of PRL on the pancreas results in augmented insulin secretion (Sorenson et al. 1987). PRL is also reported to have a direct effect on

adrenal steroidogenesis. It increases androgens, dehydroepiandrosterone (DHEA), and also cortisol and aldosterone secretion by the adrenal cortex cells (Bole-Feysot et al. 1998; Freeman et al. 2000). In mammals PRL is involved in osmoregulation: it reduces renal Na+ and K+ excretion and stimulates Na+-K+ adenosine triphosphatase activity in the outer medulla of the rat kidney (Pippard and Baylis 1986; Richardsson 1973). Newer investigations show that PRL has an inhibitory effect on Na+-K+-ATPase of rat proximal tubular cells via interaction with renal dopaminergic system (Crambert et al. 2010; Ibarra et al. 2005). Furthermore, PRL increases sodium and chloride ion excretion with sweat and increases water and salt absorption in all segments of the intestine. Ultimately, it causes a reduction of water transport in the human amniotic membrane (Bole-Feysot et al. 1998; Freeman et al. 2000).

The autocrine and the paracrine actions of PRL locally synthesized by lymphocytes seem to have functional significance (Chavez-Rueda et al. 2005). In vitro investigations of human mononuclear cell cultures have shown that PRL alone is unable to induce proliferation of lymphocytes. However PRL acts as a co-stimulating factor for T lymphocytes, activated by an unspecific mitogen (concanavalin A) or by antigen presentations (Chavez-Rueda et al. 2005). The addition of neutralizing antibodies against PRL to the peripheral mononuclear cell cultures significantly decreases the activation and proliferation of T lymphocytes (Chavez-Rueda et al. 2005). It indicates that PRL is secreted locally by activated and proliferating T-cells and that it affects the proliferation on the basis of a positive reciprocal circuit (Chavez-Rueda et al. 2005).

PRL has over 300 described functions, but the clinical relevance is unclear as there is still no clearly recognized deficiency syndrome (Harvey et al. 2008). However, recent and emerging evidence shows that low PRL levels are associated with different pathological correlates and, for this reason, hypoprolactinemia may deserve a specific chapter in clinical manuals, as a new clinical syndrome.

Causes of Hyperprolactinemia

A number of physiological states including pregnancy, breastfeeding, stress, exercise, meals, sleep, and sexual intercourse can cause PRL elevation, as can medication and some pathological conditions (Table 1).

Pathophysiologic causes of HPRL include lactotroph adenomas, stalk disruption, primary hypothyroidism, and renal failure. However, the most frequent non-physiological HPRL cause is drug exposure.

Although the levels can hint at the etiology of the HPRL, there is significant overlap in the figures among different etiologies; this is especially true among those that are normally seen in microprolactinomas and in those secondary to drugs (Fig. 1).

Lactotroph Adenomas

PRL-secreting adenomas (lactotroph adenomas or prolactinomas) are pituitary adenomas that express and secrete PRL to variable degrees, are almost invariably

Table 1 Etiology of hyperprolactinemia

Physiological
Pregnancy and lactation
Sleep
Stress
Coitus
Exercise
Pharmacological
Anesthetics
Anticonvulsant
Anti-H2 histaminergic antagonists
Antihypertensive
Catecholamine depletors
Cholinergic agonists
Dopamine receptor blockers
Dopamine synthesis inhibitors
Estrogens
Neuroleptics/antipsychotics
Neuropeptides
Opiates and opiate antagonists
Tricyclic antidepressants
Pathological
Prolactinoma
Mixed adenoma
Pituitary or hypothalamic diseases with damage/interruption of the stalk
Pituitary mass
Inflammatory or granulomatous diseases
Trauma
Surgery
Radiotherapy
Empty sella
Primary hypothyroidism
Chronic renal failure
Polycystic ovarian disease
Liver cirrhosis
Neurogenic chest wall trauma, surgery, herpes zoster
Paraneoplastic syndrome
Idiopathic hyperprolactinemia

benign, but are nevertheless frequently clinically significant and may be challenging to manage. Prolactinomas are generally classified according to size as micro-adenomas (less than 10 mm in diameter) or macroadenomas (more than 10 mm in diameter). Over 90% of prolactinomas are small, intrasellar tumors that rarely increase in size (Molitch 1995). Occasionally, these adenomas can be aggressive

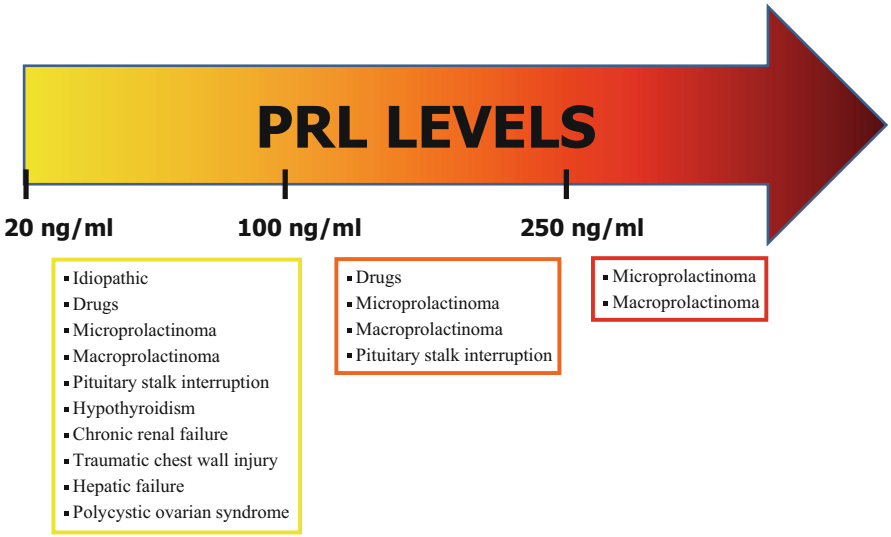

Fig. 1 Levels of PRL vary in function of the different aetiologies of the hyperprolactinaemia

or locally invasive and cause compression of vital structures. Malignant prolactinomas that are resistant to treatment and disseminate inside and outside the central nervous system (CNS) are very rare.

PRL levels typically correlate with tumor size. Individuals with large adenomas can have PRL levels on the order of 10^4 ng/ml (Delgrange et al. 1997), yet with poorly differentiated or cystic lesions, PRL levels will be lower than expected based on size.

It is not known how prolactinomas develop, but the process may involve an early genome mutation that results in a mutated pituitary stem cell. Various permissive factors may then stimulate the proliferation of these mutated cells. Familial prolactinomas have also been described (Sobrinho 1995) suggesting that a genetic component might contribute to the pathogenesis.

Prolactinomas are the most common subtype of secretory pituitary adenoma, accounting for approximately 40% of all pituitary tumors. The reported population prevalence of clinically apparent prolactinomas ranges from 6–10 per 100,000 to approximately 50 per 100,000 (Daly et al. 2006; Fernandez et al. 2010). In an analysis of 1607 patients with medically treated HPRL, 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 years (Kars et al. 2009).

Stalk Disruption

Because PRL secretion is tonically inhibited by hypothalamic DA, disruption or compression of the pituitary stalk by traumatic injuries or a non-PRL-secreting

pituitary tumor or other parasellar mass will lead to HPRL: the so-called stalk effect. Usually serum PRL does not exceed 100 ng/ml in this setting (Karavitaki et al. 2006), but exceptions do occur.

Patients with large pituitary tumors, craniopharyngiomas, or granulomatous infiltration of the hypothalamus can develop HPRL because of pituitary stalk compression or dopaminergic neuronal damage. In 226 patients with histologically confirmed nonfunctioning pituitary macroadenomas, a PRL level greater than 94 ng/ml reliably distinguished between prolactinomas and nonfunctioning adenomas (Karavitaki et al. 2006).

It has been shown that successful surgical resection of nonfunctioning pituitary adenomas where DA delivery is restored results in rapid normalization of PRL levels (Arafah et al. 1995).

It is important to determine in the presence of a pituitary adenoma whether patients with HPRL also have acromegaly (Bonert and Melmed 2006) because PRL is elevated in up to 50% of patients with GH-secreting tumors (Kleinberg et al. 1977). This may be related to both the "stalk effect" due to a GH-secreting adenoma and the presence of a mixed adenoma secreting both GH and PRL.

Primary Hypothyroidism

Some patients with primary hypothyroidism may have moderate HPRL (Honbo et al. 1978; Molitch 1992). It has been proposed that this is due to the increased synthesis of, or sensitivity to, hypothalamic TRH, which is able to stimulate pituitary lactotroph cells, but the true cause is still unknown. Long-lasting or inadequately treated primary hypothyroidism can cause pituitary hyperplasia that may mimic a pituitary tumor. In this case, particular care should be taken to distinguish pituitary enlargement from prolactinoma. Treatment with L-thyroxine can reverse HPRL and enlargement of the pituitary gland due to thyroid failure (Ahmed et al. 1989; Keye et al. 1976).

Chronic Renal Failure

Patients with renal insufficiency may have moderate HPRL caused by impaired renal degradation of PRL and altered central PRL regulation (Hou et al. 1985; Lim et al. 1979). The latter may be the result of reduced lactotroph responsiveness to DA suppression (Sievertsen et al. 1980).

Drug-Induced Hyperprolactinemia

The most frequent nonphysiological HPRL cause is drug exposure, and, among all of them, the antipsychotics are the main culprits by far with respect to all the others (Kinon et al. 2003).

With drug-induced HPRL, PRL levels increase slowly after oral administration, and it usually takes 3 days for levels to return to normal after drug discontinuation

(Pollock and McLaren 1998; Spitzer et al. 1998). Medication-induced HPRL is usually associated with PRL levels ranging from 25 to 100 ng/ml, but metoclopramide, risperidone, and phenothiazines can lead to PRL levels exceeding 200 ng/ml (Smith et al. 2002a; Meltzer and Fang 1976) (Fig. 1).

The mechanism of antipsychotic-induced HPRL relates to the DA antagonist effect of these drugs on the D2 receptors of the TIDA system and lactotrophs (Molitch 2005a; Green and Brown 1988). By blocking the interaction between DA and the D2 receptors, the tonic inhibition of PRL secretion is negated, and increased PRL secretion results. This explains why antipsychotics with a greater D2 occupation index produce higher and more frequent PRL elevations. This is the case of risperidone and its 9-hydroxymetabolite paliperidone (Bellantuono and Santone 2012; Chwieduk and Keating 2010; Janicak and Winans 2007) considered the second-generation antipsychotics that cause HPRL most often, with levels even higher than those of haloperidol (Kinon et al. 2003). Another action mechanism involved is their ability to cross the blood-brain barrier: risperidone and paliperidone remain the longest outside of the barrier due to their low liposolubility; consequently, they act for a longer period in the TIDA pathway, provoking HPRL (Besnard et al. 2014). The stable link between HPRL and the use of risperidone, paliperidone, amisulpride, and the majority of the first-generation antipsychotics has led to this group being called "PRL-raising" or hyperprolactinemic antipsychotics in the literature. A study on 158 treatment-resistant patients that compared the PRL levels of various antipsychotics estimated that 60–100% of the women and 40–80% of the men treated with hyperprolactinemic antipsychotics presented HPRL (Volavka et al. 2004). In contrast, other atypical antipsychotics, called "PRL-sparing" antipsychotics in the literature, such as aripiprazole, asenapine, clozapine, quetiapine, and ziprasidone present a better profile with respect to limited PRL increase (Byerly et al. 2007; Cruz and Vieta 2011; Montejo et al. 2008; Smith 2008; Svestka et al. 2007).

In a recent meta-analysis on efficacy and tolerability of 15 antipsychotics, paliperidone and risperidone have been shown to be the antipsychotics most related to HPRL. Aripiprazole and quetiapine have the best hyperprolactinemic profile (Leucht et al. 2013).

In addition to antipsychotic medications, many other drugs can cause HPRL; among these verapamil causes HPRL in 8.5% of patients (Molitch 2005a), presumably by blocking hypothalamic DA. Opiates and cocaine act through the μ-receptor (Bart et al. 2003; Tolis et al. 1975; Zis et al. 1984) to cause mild HPRL (Mendelson et al. 1989). The role of estrogen in causing HPRL is controversial (Molitch 2005a). Twelve to 30% of women taking higher estrogen-containing oral contraceptives may have a small increase in serum PRL, but this finding is rarely an indication for therapy (Luciano et al. 1985).

Other Pathological Conditions Characterized by Hyperprolactinemia

Traumatic chest wall injury is a rare potential cause of HPRL (Morley et al. 1977). In a patient with HPRL after a severe burn to the chest wall, intercostal nerve blockade

resulted in normalization of her serum PRL level (Morley et al. 1977), suggesting that a neurogenic stimulus at the site of injury was responsible.

Hepatic failure is a cause of HPRL usually due to decreased clearance of PRL. However recent reports suggest that it is a very rare cause of HPRL (Ress et al. 2014).

The polycystic ovarian syndrome is commonly associated with elevated PRL levels as well (Yazigi et al. 1997).

Finally, the serum PRL level usually rises following an epileptic seizure (including after electroconvulsive therapy).

Idiopathic Hyperprolactinemia

Finally, idiopathic HPRL needs to be considered as diagnosis (Casanueva et al. 2006; Melmed et al. 2011).

Fewer than 10% of patients with idiopathic HPRL ultimately are found to harbor a microadenoma, and progression from a microadenoma to a macroadenoma is rare (Sluijmer and Lappöhn 1992). Spontaneous normalization of PRL levels occurs in approximately 30% of patients with idiopathic HPRL (Schlechte et al. 1989).

Diagnosis of Hyperprolactinemia

Updated guidelines recommend a single measurement of serum PRL to establish the diagnosis of HPRL: a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress (Casanueva et al. 2006; Melmed et al. 2011). The guidelines advise against performing dynamic tests for the diagnosis of HPRL (Casanueva et al. 2006; Melmed et al. 2011); indeed dynamic tests using TRH, L-dopa, nomifensine, domperidone, and insulin-induced hypoglycemia are not superior to measuring a single serum PRL sample for the diagnosis of HPRL (Casanueva et al. 2006; Melmed et al. 2011).

When initial PRL values are not diagnostic (e.g., above the normal laboratory range, but not high enough to clearly indicate a prolactinoma), sampling should be repeated on another day. In this case, to avoid the effect of pulsatile secretion, two to three samples separated by at least 15–20 min should be obtained.

However this recommendation has been recently criticized by Szosland et al. who suggested that daily profile of PRL in any patient with clinical suspicion of HPRL was the best mode for estimating mean circadian PRL concentration, while the attempts to diagnose HPRL based on a single PRL assay failed due to a high percentage of false-negative and false-positive results (Szosland et al. 2015).

Diagnosis of the Cause of Hyperprolactinemia

When evaluating a patient with symptoms consistent with HPRL and persistently elevated serum PRL, secondary causes should first be ruled out by a careful clinical history, physical examination, pregnancy test, routine biochemical analysis (to evaluate kidney and liver function), and TSH determination (Fig. 2).

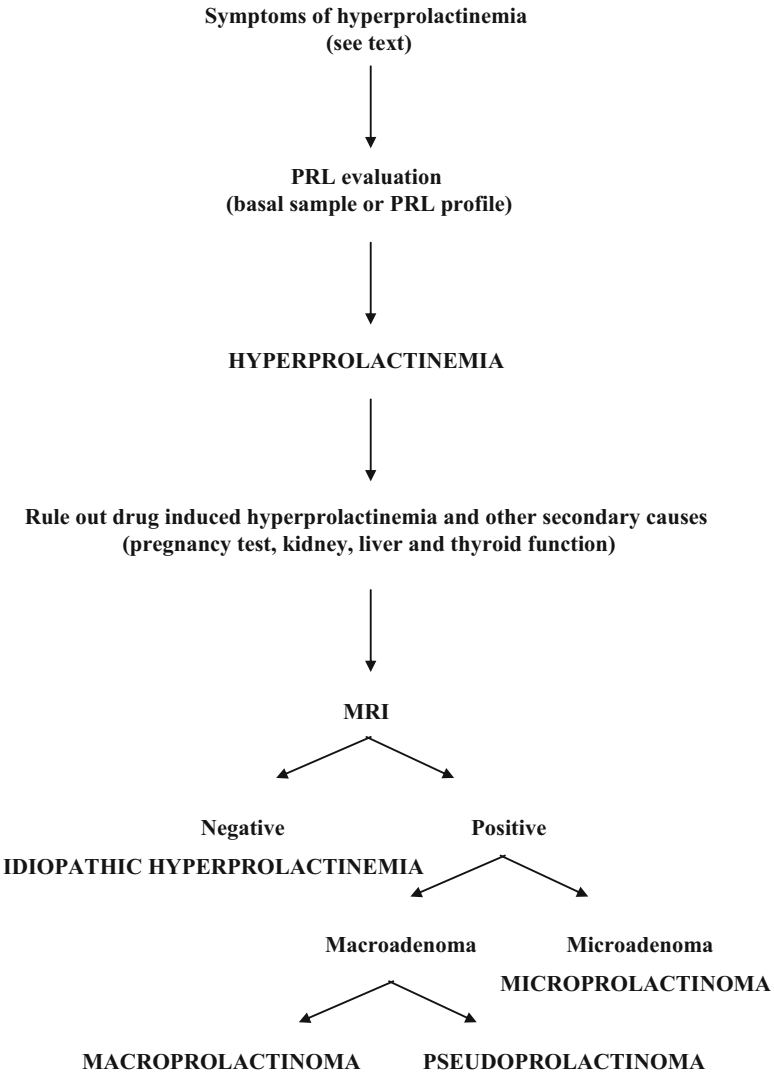

Fig. 2 Recommended diagnostic algorithm for hyperprolactinemia

If the patient is taking a drug known to cause HPRL, it is important to determine if the drug is indeed the cause by withdrawing the drug for at least 72 h, if this can be done safely. If feasible, the patient could be switched to an alternative drug that does not cause HPRL. However it is essential to discuss the issue with the prescribing physician and to obtain a psychiatric evaluation before stopping any psychiatric drugs suspected of causing HPRL. When the drug cannot be stopped, particularly in a patient with neurological symptoms, the evaluation should include magnetic resonance imaging (MRI) of the sella to exclude a mass lesion.

Although a PRL level greater than 250 ng/ml usually indicates the presence of a prolactinoma, selected drugs, including risperidone and metoclopramide, may cause PRL elevations above 200 ng/ml in patients without evidence of adenoma (Casanueva et al. 2006; Kearns et al. 2000; Melmed et al. 2011). Increases in PRL levels due to interference with DA action are usually modest, with levels rarely exceeding 150 ng/ml (Casanueva et al. 2006). However, such values are not absolute, and prolactinomas can present with variable elevations in PRL levels. Taking into account that there may be dissociation between tumor mass and hormonal secretion (Casanueva et al. 2006; Melmed et al. 2011; Mancini et al. 2008), even minimal PRL elevations may be consistent with the presence of a prolactinoma, but a non-PRL-secreting mass (pseudoprolactinoma) should first be considered (Fig. 1).

Diagnostic Pitfalls

Macroprolactin

Two high molecular mass forms of PRL have been identified by gel filtration chromatography in human serum: macroprolactin (macroPRL) (big-big PRL, >100 kDa) and big PRL (40–60 kDa). MacroPRL has a variable composition and structure but is most frequently a complex of PRL and IgG, with a molecular mass of 150–170 kDa. It is formed in the circulation following pituitary secretion of monomeric PRL but has a longer half-life, and the PRL in the complex remains reactive to a variable extent in immunoassays (Smith et al. 2002b). In the majority of subjects, little or no macroPRL can be detected in serum, but in some individuals it may be the predominant immunoreactive component of circulating PRL and the cause of apparent HPRL (Fig. 3a).

MacroPRL is an under-recognized cause of elevated PRL and is present in approximately 4% to 40% of hyperprolactinemic patients depending on the referral population (Samson et al. 2015).

Because of its high molecular weight, it is believed that macroPRL is confined to the intravascular compartment, and much evidence indicates that it has minimal bioactivity in vivo and is not of pathological significance. Therefore, a lack of recognition of the presence of macroPRL can lead to unnecessary laboratory investigations, imaging, and pharmacologic or surgical treatment.

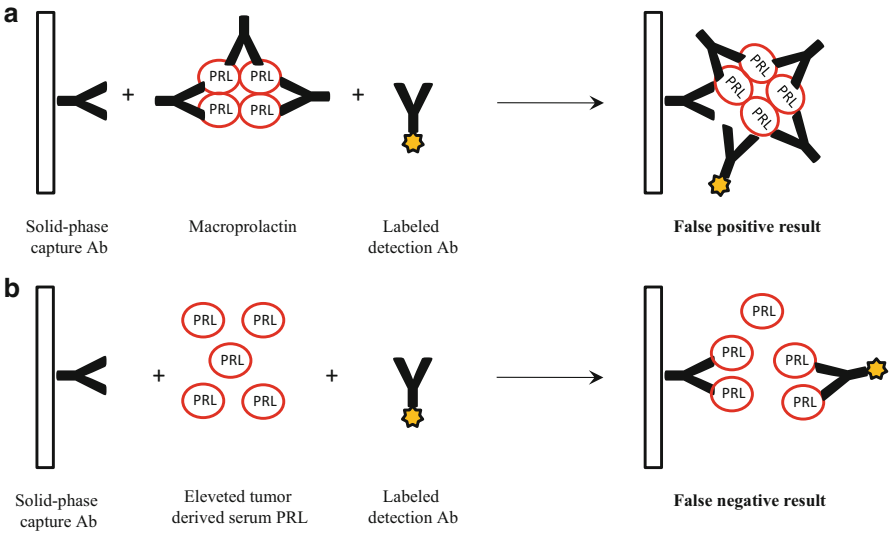

Fig. 3 Diagnostic pitfalls in hyperprolactinemic states: (**a**) **the macroprolactin problem:** if patients have circulating serum macroprolactin (preformed complexes of IgG and prolactin), with most immunoassays the sandwich formation occurs and the macroprolactin complex is therefore detected; however, because macroprolactin is bioinactive, the result is clinically misleading and constitutes a false-positive result. (**b**) **the "hook-effect" problem:** the "hook-effect" is caused by grossly elevated serum prolactin levels simultaneously saturating both the capture and detection antibodies, preventing immunoassay sandwich formation and quantitative detection of prolactin

MacroPRL is detected by most but not all PRL assays; therefore each center must know the specific characteristics of the PRL immunoassay they use. For confirmation of macroPRL, polyethylene glycol precipitation is the most practical method. Alternatively, size exclusion chromatography can be used, but is time-consuming and not suitable for routine use (Gibney et al. 2005).

In comparison with macroPRL, little is known about big PRL. It is a more consistent component of total serum PRL but rarely, if ever, the cause of HPRL.

The "Hook Effect"

Large amounts of antigen may produce falsely low values in immunoradiometric assays due to the so-called high-dose "hook effect" (Fig. 3b). Therefore, the "hook effect" may be observed when the PRL level is extremely high, as in some cases of giant prolactinomas. In this condition, extremely high levels of PRL can interfere with the assay and produce low readings. This high-dose "hook effect" may occur because there is not enough antibody to bind to both ends of PRL peptides; therefore most of the PRL is complexed to a single antibody. Only a little amount of PRL peptides are "sandwiched" and detectable. This results in a falsely low PRL value (St-Jean et al. 1996; Unnikrishnan et al. 2001; Yener et al. 2008). Hence, as the

antigen concentrations increase, there is a proportional increase in assay titers up to a certain level. Antigen concentrations above this threshold level would "hook" down the assay values resulting in very low measurements (Unnikrishnan et al. 2001; Yener et al. 2008). In addition, high-antigen titers can directly dissolve the antigen-antibody complex (Unnikrishnan et al. 2001). To overcome the "hook effect," an immunoradiometric PRL assay should be performed at a serum dilution at 1:100 or alternatively should include a washout between the binding to the first antigen and the second step in order to eliminate excess unbound PRL (Casanueva et al. 2006).

The immunoradiometric PRL assay must be performed with serum dilution in order to overcome the high-dose PRL "hook effect" in all new patients with large pituitary macroadenomas who have normal or mildly elevated PRL levels (Casanueva et al. 2006). Though repeatedly demonstrated in other immunoassays, the high-dose "hook effect" has only occasionally been observed in chemiluminescence assay systems for PRL estimation (Unnikrishnan et al. 2001).

Clinic of Hyperprolactinemia

The clinical consequences of pathological increased PRL levels can reveal themselves in the short, medium, and long term. The most immediate effects occur on sexual and gonadal function and on the breast, in both females and males. The long-term consequences are to a great extent conditioned by the permanence of these effects over time. However, they are also likely to be a consequence of other direct pleiotropic effects of PRL on different organs and tissues.

Hypogonadism

Pathological HPRL, whether or not it arises from a structural pituitary or hypothalamic lesion, is an important cause of reproductive dysfunction in both genders (Walsh and Pullan 1997).

In general, the degree of hypogonadism is proportional to the degree of PRL increase.

The exact mechanism by which HPRL causes hypogonadotropic hypogonadism is not known, but hyperprolactinemic women have reduced luteinizing hormone (LH)-pulse frequency and reduced LH responsiveness to estrogen (Matsuzaki et al. 1994; Sauder et al. 1984; Winters and Troen 1984), suggesting that GnRH suppression may be a key factor. CRH (Kooy et al. 1990) and kisspeptin, a protein made by neurons in the arcuate and periventricular nuclei of the hypothalamus, which stimulates GnRH release (Brown et al. 2014), may be important mediators of PRL-induced GnRH suppression. In rodent models, PRL receptor mRNA has been localized to kisspeptin neurons in the hypothalamus (Kokay et al. 2011), and kisspeptin administration to hyperprolactinemic female mice increases circulating gonadotropin levels and restores ovulation (Sonigo et al. 2012). HPRL has been associated with loss of the positive estrogen feedback on gonadotropin secretion at

mid-cycle (Glass et al. 1975), but whether this effect is mediated through kisspeptin is not known. Moreover, PRL also directly suppresses progesterone and estrogen secretion from human ovaries (Demura et al. 1982). PRL can decrease estrogen levels through direct effects on ovarian aromatase activity and by blocking the stimulatory effects of follicle-stimulating hormone (FSH) (Dorrington and Gore-Langton 1982; Krasnow et al. 1990). Although at low levels (<20 ng/ml) PRL is necessary for progesterone production in granulosa cell, at hyperprolactinemic levels it inhibits progesterone production (McNatty 1979). Direct PRL effects on ovarian granulosa cells include stimulation of the expression of type 2 3β-hydroxysteroid dehydrogenase (HSD), the enzyme responsible for catalyzing the final step in progesterone biosynthesis and the secretion of insulin-like growth factor 2 (IGF-2) (Feltus et al. 1999; Ramasharma and Li 1987).

Typically in women, menstrual disturbance occurs which may range in severity from luteal phase insufficiency with otherwise regular menses (Seppala et al. 1976) to irregular or infrequent periods (oligomenorrhea) and to amenorrhea. The oligo-amenorrhea in women is associated with infertility which is generally reversible upon restoration of normal PRL levels. In a compilation of three series of infertile women (total 367), approximately one-third had HPRL (Molitch and Reichlin 1982). That PRL excess may be important in this type of patient is suggested by the finding that treatment of similar patients with bromocriptine, a DA agonist, restored fertility (Skrabanek et al. 1980). Transient HPRL lasting for 1–2 days during the cycle has been shown in some infertile women, and such women may respond to DA agonists with increased progesterone during the luteal phase and improved fertility (Huang et al. 1991). Galactorrhea may also occur, alone or in combination with menstrual disturbance (Glass et al. 1975). Finally, in females due to hypogonadism there can be dyspareunia secondary to vaginal dryness.

In men, HPRL usually results in loss of libido and erectile dysfunction as a result of testosterone deficiency (Pinzone et al. 2000; Walsh and Pullan 1997). The combination of lowered libido with erectile dysfunction is the most frequent pattern in males with HPRL. Delay in or lack of orgasm can be associated with this pattern or, more rarely, present alone. The sexual dysfunction observed in hyperprolactinemic patients would be greatly conditioned by the situation of hypogonadism secondary to HPRL, although there are also data in favor of a direct HPRL effect on the libido and on erectile dysfunction (Buvat et al. 2006; Corona et al. 2007), probably mediated by the dopaminergic system (Drago et al. 1981). At local level, the erectile dysfunction would be related to endothelial dysfunction secondary to decreased nitric oxide (NO) production from inhibition of endothelial NO synthetase (Montes de Oca et al. 2005; Yu-Lee 2002) and vasoconstriction from β2-adrenergic effect (Molinari et al. 2007).

The role of PRL in male reproduction and fertility has been studied in several animal models, leading, however, to conflicting results. PRL receptor is expressed in the testis of rodents and mammals (Bole-Feysot et al. 1998), including men (Hair et al. 2002). In particular, PRL receptor expression has been demonstrated in Leydig, Sertoli, and germ cells (Ishida et al. 2010; Jabbour and Lincoln 1999). PRL can affect steroidogenesis by modulating the expression of LH receptors

(Dombrowicz et al. 1992; Takase et al. 1990) or by regulating the activity of steroidogenetic enzymes (Chandrashekar and Bartke 1988; Rubin et al. 1976), such as 5α-reductase, 3β-HSD, and 17β-HSD (Gunasekar et al. 1988; Takeyama et al. 1986). In animal models, PRL regulates spermatogenesis as well. PRL induces the expression of FSH on Sertoli cells and stimulates the progression of germ cells from spermatocyte to spermatide morphology (Gunasekar et al. 1991).

In men, studies on the effects of PRL on fertility are scanty, and, since mutations in PRL gene have not been described and mutations in PRL receptor were found only in women (Newey et al. 2013), no model of spontaneous defective PRL action is available. A study conducted in human sperms suggested that PRL is involved in the survival of these cells, since, after incubation with PRL, their motility was preserved for a longer time and spontaneous DNA strand fragmentation was decreased (Pujianto et al. 2010). However, a recent study conducted on 269 male partners of infertile couples failed to demonstrate any significant association between semen parameters and serum PRL levels (Lotti et al. 2013).

PRL has also a trophic effect on male seminal accessory glands. PRL and its receptor are expressed in the prostate, and studies in vitro and in vivo demonstrated that their regulation is androgen dependent (Nevalainen et al. 1997a). Moreover, PRL seems to be involved also in the secretory activity of male accessory glands; in fact the increase or suppression of PRL levels has been associated with a change in seminal vesicle and prostate secretion composition in different animal models (Arunakaran et al. 1988; Nicoll 1980; Ravault et al. 1977). PRL receptor expression has been demonstrated in human seminal accessory glands (Hair et al. 2002; Nevalainen et al. 1997b). However, the clinical implication of PRL activity on the male genital tract is still unclear.

Effects of Hyperprolactinemia on Calcium Metabolism and Bone

In both genders, HPRL and the resulting deficiency of sex steroid may lead to bone loss and osteoporosis (Greenspan et al. 1986; Klibanski et al. 1980). While correction of the elevated PRL improves bone density (Klibanski and Greenspan 1986), it seems that the bone loss is not directly mediated by the elevated PRL and restoration of sex steroid concentrations is required for subsequent improvement in bone density, even in the presence of ongoing HPRL (Greenspan et al. 1989). However, some experimental studies point to a possible direct adverse effect of PRL on osteoblastic function (Seriwatanachai et al. 2009). This would explain the finding in some clinical studies of a greater bone mineral density (BMD) deterioration in amenorrheic females with HPRL compared to normoprolactinemic females with similar estradiol levels and duration of amenorrhea (Schlechte et al. 1987), as well as the greater risk of vertebral fractures in males with HPRL, regardless of testosterone values (Mazziotti et al. 2011). Genetic evidence has shown that the PRL receptor is essential to normal bone formation and calcium homeostasis (Klibanski and Greenspan 1986). PRL receptor-deficient mouse displayed reductions in BMD and bone mineral content, as well as a deceleration in the apposition rate for new bone. Plasma

total calcium and parathyroid hormone were each higher in the receptor-deficient mice. The phenotypic characteristics of bone growth and calcium homeostasis in PRL receptor-deficient mice argue that there must be multiple sites of PRL action that influence calcium metabolism, including both direct effects on bone cells and systemic actions on other hormones or carriers.

Effects of Hyperprolactinemia on Cancer Risk

It seems that certain basically hormone-dependent tumors, such as those of the breast, may be related to the molecular signaling pathway of the PRL receptors.

Despite the limitations and the impossibility of having type I levels of evidence or clinical trials on the matter, there are an important number of studies, both experimental and epidemiological, that indicate that the increased PRL plasma levels seem to be related to increased risk of cancer, fundamentally breast cancer, especially in postmenopausal women (Clevenger et al. 2003; Faupel-Badger et al. 2014; Goffin et al. 2005; Hankinson et al. 1999; Harvey et al. 2006; Manjer et al. 2003).

In vitro studies have shown that PRL is mitogenic (Harvey et al. 2006), but a recent Dutch study showed no increase in breast cancer rate in women with idiopathic HPRL or prolactinomas (Dekkers et al. 2010a).

Furthermore, surgical series of breast cancer patients noted HPRL in a similar number of women with benign breast conditions as breast cancer (Nicol et al. 2002).

No increased risk of breast or prostate cancer was observed in hyperprolactinemic patients with prolactinomas (Berinder et al. 2011).

Therefore, although some epidemiologic studies suggest that HPRL is a risk for breast and prostate cancer, there is inadequate evidence to conclude a significant causal association between HPRL and cancer.

Effects of Hyperprolactinemia on Cardiovascular Diseases

HPRL has been associated with long-term cardiovascular effects, mainly mediated by sexual steroid deficit and by direct PRL action at cardiovascular level.

In vitro studies have shown that PRL per se is capable of modulating inflammatory response (Erem et al. 2010; Friedrich et al. 2011; Shibli-Rahhal and Schlechte 2009) and producing endothelial dysfunction by reducing NO production (Molinari et al. 2007; Montes de Oca et al. 2005; Yavuz et al. 2003; Yu-Lee 2002). PRL could also stimulate angiogenesis indirectly, as it encourages the synthesis of substances such as endothelial growth factor and fibroblast growth factor (Goldhar et al. 2005; Malaguarnera et al. 2002) stimulating the proliferation of smooth muscle cells of the vascular wall and the adhesion of mononuclear cells to vascular endothelium. In addition, PRL has been related to an increase in platelet aggregation (Wallaschofski et al. 2001), as well as to increased intima-media thickness at carotid level, compatible with preclinical atherosclerosis

(Arslan et al. 2014). Lastly, PRL receptor expression has been demonstrated in macrophages within atheroma plaque (Reuwer et al. 2009, 2011).

In women with early menopause, a correlation between PRL levels, blood pressure, and artery wall rigidity has been shown; this could indicate an acceleration of the atherosclerotic process with increased calculated risk of cardiovascular mortality at 10 years (Georgiopoulos et al. 2009). Recently, in a cohort study that included 3929 males and females followed for 10 years, a positive correlation between PRL levels and cardiovascular mortality was found in both sexes (Montejo 2008).

Effects of Hyperprolactinemia on Metabolism

There is also limited evidence that HPRL directly influences glucose and lipid metabolism (Ben-Jonathan et al. 2006).

Some clinical trials (Serri et al. 2006; Yavuz et al. 2003) carried out in a limited number of patients indicate the existence of insulin resistance in patients with HPRL that improves following treatment with bromocriptine. In vitro studies have also demonstrated the potential influence of PRL in the development of the pancreatic β-cells and in the secretion of insulin (Brelje et al. 2004; Freemark et al. 2002).

The association between HPRL and dyslipidemia has also been described (Erem et al. 2010). The PRL receptors are expressed in human adipose tissue (Brandebourg et al. 2007) where PRL reduces lipoprotein lipase activity and inhibits adiponectin secretion, leading to insulin resistance (Ling et al. 2003; Mingrone et al. 2008).

However, some authors find no correlation between PRL levels and different metabolic syndrome parameters (Ernst et al. 2009) or obtain insufficient evidence that the levels of PRL play a causal role as a risk factor for the development of metabolic syndrome or type 2 diabetes (Balbach et al. 2013).

HPRL has also been associated with ponderal increase, not always reversible, when PRL levels are normalized through drug treatment (Creemers et al. 1991; Delgrange et al. 1999; Doknic et al. 2002). Factors such as reduced dopaminergic tone, leptin resistance, or reduced adiponectin levels have been suggested for its pathogenesis (Nilsson et al. 2005).

Effects of Hyperprolactinemia on the Immune System

PRL receptors are found on a majority of immune precursor and effector cells in each of the major hematopoietic organs (bone marrow, spleen, thymus). PRL can potentiate the growth and effector function of lymphoid and myeloid cells, and hematopoietic cytokine receptors and signal transducers are closely related to those used by PRL.

In a rat model of immunodepression following acute hemorrhagic shock, PRL stimulated immune effector cell functions, as well as normal cytokine secretion (Zellweger et al. 1996). Whereas PRL can act as a positive stimulus for immune

cells when given to animals by injection, or to cells in culture, PRL deficiency does not significantly impair immune function or hematopoiesis (Horseman et al. 1997).

Several authors have described an association between HPRL and different autoimmune diseases, such as diabetes mellitus type 1, rheumatoid arthritis, and systemic erythematous lupus, among others (Atasoy et al. 2006; De Bellis et al. 2005; Leanos-Miranda and Cardenas-Mondragon 2006; Poyraz et al. 2008; Vera-Lastra et al. 2002). The physiopathological mechanism could be mediated by the antiapoptotic effect of PRL in the B lymphocytes (Orbach and Shoenfeld 2007; Shelly et al. 2012) and the stimulation of interferon-γ and interleukin-2 production by the T lymphocytes (De Bellis et al. 2005).

Effects of Hyperprolactinemia on the CNS

A recent study in a female population indicates that HPRL could have direct negative effects on cognitive function (Henry and Sherwin 2012), which could originate in low levels of gonad steroids (Craig et al. 2007, 2008; Grigorova et al. 2006; Phillips and Sherwin 1992). It has also been observed that in males low levels of testosterone are related to deterioration of the memory and of the visual-spatial abilities (Beer et al. 2006; Moffat et al. 2002; Pinsky and Hellstrom 2010) and with a greater risk of dementia (Moffat et al. 2004).

HPRL has also been associated with some psychiatric alterations, above all in females (Fava et al. 1983). Greater rates of hostility, anxiety, depression, and dysthymia have been reported in patients with HPRL (Oliveira et al. 2000; Reavley et al. 1997). The mechanism by which they would originate is unclear and is probably related to hypogonadism (Prabhakar and Davis 2008; Sobrinho 1998).

Treatment

The objective of HPRL treatment is to correct the clinical consequences of the hormonal excess. The primary goal of therapy in patients with HPRL is to restore gonadal and sexual function by normalizing PRL levels, but in patients with macroadenomas, control and reduction of tumor size are also important.

Indications for treatment include infertility, a pituitary tumor with neurological effects (particularly visual defects), bothersome galactorrhea, long-standing hypogonadism, alterations in pubertal development, and prevention of bone loss because of hypogonadism. Occasionally, patients with mild HPRL with regular menses who wish to become pregnant may also require treatment. HPRL will prove self-limiting in up to one-third of women, and in others pregnancy may induce a return to normal PRL function (Jeffcoate et al. 1996; Schlechte et al. 1986).

Women with HPRL who pass through menopause may normalize their PRL levels, and therefore in such women, reassessment of the need for continuing treatment of HPRL is indicated (Karunakaran et al. 2001).

Premenopausal women with normal menstrual cycles and tolerable galactorrhea, and postmenopausal women with tolerable galactorrhea who have idiopathic HPRL or microprolactinoma, should be reassured and not actively treated (Casanueva et al. 2006; Melmed et al. 2011).

Pharmacological Treatment

DA agonist is the therapy of choice to lower PRL levels, decrease tumor size, and restore gonadal function for patients harboring PRL-secreting macroadenomas. Asymptomatic patients harboring microprolactinomas should not be treated with DA agonists. Treatment with a DA agonist or oral contraceptive should be considered in patients with amenorrhea caused by a PRL-secreting microadenoma.

All DA agonists are efficacious, but pergolide and quinagolide are less commonly used. Cabergoline is recommended in preference to other DA agonists because it has higher efficacy in normalizing PRL levels, as well as a higher frequency of pituitary tumor shrinkage.

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 DA receptor binding sites. Moreover, because the incidence of unpleasant side effects is lower with cabergoline, drug compliance may be superior for this medication (Verhelst et al. 1999). No clinical trials have directly compared the mass-reducing effects of different DA agonists. Nevertheless, results of various studies (Molitch et al. 1985) indicate that bromocriptine decreases pituitary tumor size by approximately 50% in two-thirds of patients, compared with a 90% decrease with cabergoline.

Nevertheless, bromocriptine has been used satisfactorily for years (Molitch et al. 1985), and since it is less expensive, it should be considered in medical settings with limited budgets.

Therapy with bromocriptine (tablet of 2.5 mg) is initiated with a dose of 0.625–1.25 mg daily and increased by 1.25 mg at weekly intervals until a dose generally of 2.5 mg twice or thrice daily is reached. Side effects such as upper gastrointestinal disturbances and postural hypotension can be reduced by using an incremental dosage schedule and taking tablets with a snack before retiring. Cabergoline (tablet of 0.5 mg) therapy is begun at a dose of 0.25–0.5 mg administered once or twice weekly, and the dose is increased monthly until PRL secretion normalizes (Schlechte 2003; Webster et al. 1994). Doses over 3 mg per week are rarely necessary.

Patients who are resistant to, or who cannot tolerate, a particular DA agonist should be switched to an alternative DA agonist (Colao et al. 1997). Cabergoline is effective in most patients, including those who did not previously respond to bromocriptine (Colao et al. 1997).

For patients with medication-induced HPRL, the primary treatment is to stop the drug or to switch to an alternative drug. For antipsychotic-induced HPRL, alternative medications include antipsychotic agents with lower DA antagonist potency

(Kinon et al. 2003; Volavka et al. 2004) or aripiprazole, an atypical antipsychotic with both DA agonist and DA antagonist activity (Lu et al. 2008) that can lower PRL and reverse HPRL-related side effects (Saitis et al. 2008). 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 (Bhasin et al. 2010; Casanueva et al. 2006; Melmed et al. 2011).

Whether to treat a patient who has antipsychotic-induced HPRL with a DA agonist remains controversial. Some studies suggest that DA agonist therapy will normalize PRL levels in only up to 75% of such patients but may lead to exacerbation of the underlying psychosis (Cavallaro et al. 2004; Cohen and Biederman 2001; Smith 1992; Tollin 2000); therefore in such situations treatment with DA agonists should be considered only after careful psychiatric counselling (Casanueva et al. 2006; Melmed et al. 2011).

In an asymptomatic patient with medication-induced HPRL, no treatment is necessary.

Surgical Treatment

It is widely accepted that pharmacological treatment is the first choice for PRL-secreting pituitary adenoma, but surgery remains a good therapeutic option in patients intolerant or resistant to DA agonists or in cerebrospinal fluid leaks post tumor shrinkage (Kreutzer et al. 2008; Nomikos et al. 2001). With the advancement of surgical techniques, surgical intervention may be a reasonable option in microprolactinoma when the patient opts for surgical resection rather than medical management (Babey et al. 2011; Couldwell and Weiss 2004).

Surgery is also indicated for individuals with cystic tumors which do not respond to DA agonist therapy, tumors causing mass effect (cranial nerve palsies, visual impairment) which is not relieved by medical treatment, in case of intratumoral hemorrhage with mass effect or apoplexy requiring emergent/urgent decompression of the optic chiasm to preserve visual function on DA therapy.

Pituitary transsphenoidal surgery is associated with very low mortality (<1%) and very low morbidity rates. Both the expertise and experience of the neurosurgeon and the volume of the surgical center also play a role in these low rates of complications (Ikeda et al. 2013). Side effects of surgery include hypopituitarism, diabetes insipidus, cerebrospinal fluid leak, and local infection (Melmed et al. 2011).

Clinical results and economic costs of surgical resection are comparable to those of pharmacological management over a 10-year period. This suggests that surgery may be a more cost-effective option than lifelong medical therapy, especially in young patients (Amar et al. 2002).

Transsphenoidal surgery is an effective modality in the management of prolactinomas for patients with indications as described above (Table 2). Long-term chemical cure rates for microprolactinomas exceed 90% when performed by experienced pituitary surgeons (Amar et al. 2002; Buchfelder and Schlaffer 2009).

Table 2 Indication for neurosurgery in PRL-secreting pituitary adenomas

Intolerance to dopamine agonists
Resistance to dopamine agonists
Cerebrospinal fluid leaks post tumor shrinkage
Patient's preference (microprolactinoma)
Cystic tumors which do not respond to dopamine agonist therapy
Tumors causing mass effect (cranial nerve palsies, visual impairment) which is not relieved by medical treatment
Intratumoral hemorrhage with mass effect on dopamine therapy
Apoplexy requiring emergent/urgent decompression of the optic chiasm to preserve visual function

Postoperative hormonal levels are predictive for long-term cure; in fact, PRL levels lower than 10 ng/ml on postoperative day 1 demonstrated cure rates of up to 100% in microprolactinoma patients (Amar et al. 2002).

Surgical resections for macroprolactinomas are not as successful as for microprolactinomas in terms of biochemical cure rate. Cure rates drop to <50% for macroprolactinomas (Buchfelder and Schlaffer 2009). For macroprolactinomas, both the size and baseline PRL level serve as a predictor of surgical success. In a large microscopic transsphenoidal surgical series, the rate of recurrence was over 70% when preoperative PRL levels were over 250 ng/ml (Amar et al. 2002). The objective of surgical intervention for macroprolactinomas is mainly to debulk the tumor to relieve symptoms due to mass effect and as a cytoreductive strategy, rather than to cure them. Surgically decreasing the size of a large tumor may also help increase its responsiveness to DA agonist treatment. In patients with macroprolactinomas resistant to cabergoline, surgical debulking resulted in significantly lower postoperative PRL levels at significantly lower doses of cabergoline (Vroonen et al. 2012).

Radiotherapy

External radiation is rarely required to treat prolactinomas because it is associated with significant precious and delayed side effects as impairment of pituitary secretion, risk of optic chiasma damage, cognitive and neurological dysfunction, and increased incidence of stroke and secondary brain neoplasms.

Radiotherapy is therefore suggested as a third-line treatment for prolactinomas that are refractory to medical therapy or surgery, mainly for tumor growth control.

In Western countries radiotherapy means stereotactic technique, while conventional approach is completely abandoned and should be avoided.

With the advances in high-resolution imaging, image guidance, and dosage planning, stereotactic radiotherapy has been demonstrated to be relatively well tolerated with excellent accuracy and safety profiles (Wong et al. 2015).

Stereotactic Radiosurgery (SRS): Gamma Knife

During the past two decades, SRS has become a frequently used radiation technique because of its convenience, more rapid correction of hormone oversecretion (Kong et al. 2007), and a lower risk of radiation-induced neoplasms and carotid stenosis (Cohen-Inbar et al. 2015). SRS provides a highly conformal and selective therapeutic intervention in a single procedure performed with image guidance, achieving maximal precision. Such an approach reduces the long-term risk of larger-field radiotherapy.

There are only a few studies showing the effect of SRS on prolactinomas as a first-line treatment (Pan et al. 2000). A limit to Gamma Knife use as a primary treatment is that a number of studies have shown that radiosurgery is less effective in achieving endocrine remission for prolactinomas than for other types of pituitary adenoma patients. Clinical control was reported in 17–47% (Jezkova et al. 2009; Cohen-Inbar et al. 2015) though it has been reported even better control (52%) (Castinetti et al. 2009) in tumor mass effect; control rate has been reported higher than 95% if the follow-up time has been long enough (60–120 months).

Treatment Pitfalls

Pregnancy

Women with HPRL who wish to become pregnant or who are pregnant should be guided through the process by an endocrinologist. In particular there are four main issues with respect to gestation and HPRL: HPRL and fertility, safety of DA agonists, tumor growth, and lactation.

Hyperprolactinemia and Fertility

When starting DA treatment, women must be warned that restoration of ovulation and fertility may be immediate and even before their first normal menstruation (Casanueva et al. 2006; Melmed et al. 2011). Indeed, treatment with DA agonists in high percentage of cases normalizes PRL levels and consequently controls symptoms PRL related, i.e., oligo-amenorrhea and infertility. For this reason, when starting DA agonist treatment, mechanical contraception should be advised, and menses may serve as a guide. This is in order to discontinue DA agonist therapy as soon as patients discover that they are pregnant and to avoid an unnecessary and excessive exposure of the fetus to the effect of DA drugs.

When a female patient with a macroprolactinoma wishes to become pregnant, it is necessary to plan conception to occur after serum PRL is normalized and the tumor volume significantly reduced in order to avoid or reduce the risk of compression of the optic chiasm during pregnancy.

Women with macroprolactinomas who are intolerant or resistant to DA agonist therapy and want to reproduce can consider surgical debulking or radiotherapy

before attempting a pregnancy (Casanueva et al. 2006; Melmed et al. 2011). However it must be considered that surgery and radiotherapy 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 (Melmed et al. 2011).

Safety of DA Agonists

Both bromocriptine and cabergoline are reported to be safely administered in premenopausal women (Casanueva et al. 2006; Melmed et al. 2011; Molitch 2015). Both drugs are not associated with increasing of abortions, ectopic/multiple pregnancies, and congenital malformations even if bromocriptine data are the most (Molitch 2015). On the other hand, guidelines recommended to discontinue DA agonist therapy once pregnancy is confirmed, usually 1–2 weeks after a missed period (Casanueva et al. 2006; Melmed et al. 2011). In selected patients with macroadenomas who become pregnant on dopaminergic therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm (Casanueva et al. 2006; Melmed et al. 2011)

The experience with pergolide and quinagolide in preparation for pregnancy is much more limited; for that reason these two drugs should not be used in this setting (Casanueva et al. 2006; Melmed et al. 2011).

Tumor Growth

During pregnancy in patients with prolactinoma, the size of pituitary adenoma may increase. The risk of increase is different in micro- or macroadenoma patients; in case of microadenoma, the risk of symptomatic growth is 3% while in macroadenoma is significantly higher being 30%; previous surgery or radiotherapy reduces this risk (2.8%) (Molitch 2015).

Therefore, DA agonists can be safely stopped in patients with microprolactinoma as soon as pregnancy has been confirmed (Casanueva et al. 2006; Melmed et al. 2011). The patients should be advised to report for urgent assessment in the event of a severe headache or visual disturbance (Casanueva et al. 2006; Melmed et al. 2011).

Options for patients with macroprolactinoma include stopping the DA agonist when pregnancy is confirmed with close surveillance thereafter or continuing the DA agonist through the pregnancy (Casanueva et al. 2006; Melmed et al. 2011).

It is not recommended to measure serum PRL levels because of their physiological increase during pregnancy and their expected increase upon discontinuation of DA agonists and to avoid uninterpretable results from laboratory tests and unnecessary testing.

If pregnancy is physiological, conducted spontaneous delivery is not contraindicated.

If visual field defects or progressive headaches develop, an MRI without gadolinium should be performed to assess changes in tumor size, and a DA agonist should be restarted if the tumor has grown significantly (Casanueva et al. 2006; Melmed et al. 2011). If the enlarged tumor does not respond to reinstitution of DA agonist

therapy, alternatives include delivery if the pregnancy is far enough advanced or transsphenoidal surgery (Casanueva et al. 2006; Melmed et al. 2011).

Lactation

There are no data to suggest that breastfeeding leads to an increase in tumor size; therefore, lactation is not contraindicated in patients harboring PRL-secreting adenomas. However, women wishing to breast-feed their infants should not be given DA agonists because the resulting decrease in serum PRL levels will impair lactation (Casanueva et al. 2006). After 3 months the end of lactation serum PRL levels should be assessed, and an MRI with contrast is indicated.

D2 Resistance

The majority of patients with prolactinomas treated with standard doses of DA agonists respond with normalization of PRL levels and a reduction in tumor size.

However, some patients do not respond satisfactorily (Molitch 2003), and some patients may have discordant responses, i.e., reduction in tumor size without normalization of PRL levels and vice versa, and others may be partially resistant and require higher than typical doses of DA agonists to achieve a response.

Although the literature is not totally consistent in defining the problem as different authors employ various definitions depending on the primary endpoints of their studies (Colao 2009; Molitch 2003), resistance to DA can be most properly described as inability to lower PRL within normal limits and to achieve a 50% reduction in tumor mass by the maximum tolerated dose of DA agonist (Gillam et al. 2006). To note that DA agonist resistance differs from intolerance, where side effects of the DA agonists preclude their use.

Microadenomas are less resistant to DA agonists than are macroadenomas, and men are more likely than women to be DA agonist resistant (Delgrange et al. 2009). The level of responsiveness depends also on the type of the DA used, and many prolactinomas that are resistant to bromocriptine respond to cabergoline therapy (Colao et al. 1997).

The mechanism of DA agonist resistance is not completely understood, and it is likely that different mechanisms underlie DA agonist resistance in prolactinomas: a decreased number of D2 receptors have been reported on resistant prolactinomas (Kukstas et al. 1991; Pellegrini et al. 1989), but this finding is not invariable (Kovacs et al. 1995). However DA receptor binding has been reported to be normal, and no DA receptor mutation has been identified in prolactinomas to date. D2 receptor isoform ratios may differ; it has been reported that resistant prolactinomas had a lower proportion of the short isoform of the D2 receptor mRNA compared to sensitive ones, while no significant difference was found between responsive adenomas and normal pituitary lactotroph cells (Caccavelli et al. 1994). Finally molecular alterations may occur downstream of the D2 receptor.

A number of therapeutic approaches may be employed when managing the resistant prolactinoma patients. These include substitution with another DA, gradual

dose augmentation to maximal efficient and tolerated levels, transsphenoidal surgery, and radiotherapy (Melmed et al. 2011). Some experimental treatments are also available, but their true clinical benefit still remains to be clearly demonstrated.

Since resistance is most prevalent among patients on bromocriptine, it is usually appropriate to switch them to another more potent DA. Quinagolide reduces PRL to normal ranges in 39–44% of bromocriptine-resistant patients and induces tumor shrinkage in about 30% of cases (Morange et al. 1996; Rohmer et al. 2000), but still a large proportion fail to respond.

Much better outcomes, however, are achieved with cabergoline. Accumulating evidence suggests that cabergoline is efficient in normalizing PRL in approximately 70–85% of patients resistant to bromocriptine and quinagolide and in 84% of patients intolerant of bromocriptine (Colao et al. 1997; Molitch 2005b; Verhelst et al. 1999). Another approach especially for cabergoline-resistant patients is the gradual dose increase, provided that the patient responds with some reduction of PRL levels to every dose adjustment (Melmed et al. 2011).

However, caution must be exhibited with protracted use of high-dose cabergoline because of the potential risk of cardiac valvular regurgitation. Even if patients with Parkinson's disease receiving at least 3 mg of cabergoline daily are at risk for moderate to severe cardiac valve regurgitation (Schade et al. 2007; Zanettini et al. 2007), 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 (Bogazzi et al. 2008; Herring et al. 2009; Kars et al. 2008; Lancellotti et al. 2008; Vallette et al. 2009; Wakil et al. 2008), and the only study that reported a 57% incidence of tricuspid regurgitation in patients treated with cabergoline also noted significant tricuspid regurgitation in the control group (Colao et al. 2008). However, in patients who require very high doses of cabergoline 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 more than 3 mg of cabergoline weekly likely will require regular echocardiographic screening (Melmed et al. 2011).

Finally, in a very small number of cases, patients who initially respond to DA therapy may later become resistant. One study reported five patients who developed late DA resistance: two after bromocriptine and three following cabergoline treatment (Behan et al. 2011). Even more rarely such secondary resistance may be caused by malignant transformation (Hurel et al. 1997). A report by Lania et al. describes a case of aggressive prolactinoma successfully treated with DA for 15 years that surprisingly evolved in clinically and biochemically active acromegaly (Lania et al. 2010). The mechanisms underlying loss of responsiveness and transformation are not yet known.

Cure

There is an ongoing debate regarding the safety of the discontinuation and the optimal duration of therapy with DA agonist in prolactinomas (Casanueva et al. 2006;

Melmed et al. 2011). It has been suggested that DA agonist withdrawal may be safely undertaken after 2–3 years in patients who have achieved normoprolactinemia and significant tumor volume reduction (Casanueva et al. 2006; Melmed et al. 2011).

A landmark study by Colao et al. had demonstrated persistent normoprolactinemia post withdrawal in the majority of the study population (66.1% of microprolactinomas, 46.8% of macroprolactinomas) (Colao et al. 2003b). In general the risk of recurrence after withdrawal has been estimated to range from 26 to 69% (Biswas et al. 2005; Kharlip et al. 2009), and all studies have shown that recurrence is predicted by PRL 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 (Kharlip et al. 2009). However, a meta-analysis of 19 studies and 743 patients by Dekker et al. demonstrated stable normoprolactinemia after DA agonist withdrawal in 32% of patients with idiopathic HPRL, 21% with microprolactinomas, and 16% with macroprolactinomas, and when the study by Colao et al. was excluded from the meta-analysis, these values decreased to 17%, 19%, and 12%, respectively (Dekkers et al. 2010b).

Some studies have shown that a longer treatment duration and the use of cabergoline were associated with a greater remission rate (Dekkers et al. 2010b; Oh and Aghi 2011), while some studies have not shown this (Anagnostis et al. 2012; Barber et al. 2011). The dosage of the DA agonist should be gradually decreased, while maintaining normal PRL levels, until the drug is completely discontinued (Melmed et al. 2011). HPRL recurrence is most commonly observed during the first 6 months to 1 year following cessation (Anagnostis et al. 2012; Barber et al. 2011; Colao et al. 2003b; Kharlip et al. 2009), and regular follow-ups are necessary. In particular, guidelines (Melmed et al. 2011) suggest that in patients for whom DA agonists have been tapered or discontinued, follow-up includes (1) measurement of serum PRL levels every 3 months for the first year and then annually thereafter and (2) MRI if PRL increases above normal levels. 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.

Conclusions

PRL is secreted by pituitary lactotroph cells. The predominant signal is inhibitory, preventing PRL release, and is mediated by DA.

Pathological HPRL may develop due to lactotroph adenomas (prolactinomas), which account for approximately 40% of all pituitary tumors, or due to pharmacological or pathological interruption of hypothalamic-pituitary dopaminergic pathways. Finally, idiopathic HPRL needs to be considered as diagnosis.

Regardless of etiology, HPRL may result in hypogonadism, infertility, and galactorrhea, or it may remain asymptomatic. Bone loss occurs secondary to HPRL-mediated sex steroid attenuation.

Testing for HPRL is straightforward, owing to the case of ordering a serum PRL measurement. Accordingly, an evidence-based, cost-effective approach to management of thus relatively common endocrine disorder is required.

References

Ahmed M, Banna M, Sakati N, Woodhouse N. Pituitary gland enlargement in primary hypothyroidism: a report of 5 cases with follow-up data. Horm Res. 1989;32:188–92.

Amar AP, Couldwell WT, Chen JC, Weiss MH. Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery. J Neurosurg. 2002;97:307–14.

Amit T, Dibner C, Barkey RJ. Characterization of prolactin and growth hormone-binding proteins in milk and their diversity among species. Mol Cell Endocrinol. 1997;130:167–80.

Anagnostis P, Adamidou F, Polyzos SA, Efstathiadou Z, Karathanassi E, Kita M. Long term follow-up of patients with prolactinomas and outcome of dopamine agonist withdrawal: a single center experience. Pituitary. 2012;15:25–9.

Arafah BM, Nekl KE, Gold RS, Selman WR. Dynamics of prolactin secretion in patients with hypopituitarism and pituitary macroadenomas. J Clin Endocrinol Metab. 1995;80:3507–12.

Arslan MS, Topaloglu O, Sahin M, Tutal E, Gungunes A, Cakir E, Ozturk IU, Karbek B, Ucan B, Ginis Z, Cakal E, Ozbek M, Delibasi T. Preclinical atherosclerosis in patients with prolactinoma. Endocr Pract. 2014;20:447–51.

Arunakaran J, Balasubramanian K, Srinivasan N, Aruldhas MM, Govindarajulu P. Effects of androgens, prolactin and bromocriptine on seminal vesicular enzymes of the pyruvate malate cycle involved in lipogenesis in castrated mature monkeys, macaca radiata. Int J Androl. 1988;11:133–9.

Atasoy M, Karatay S, Yildirim K, Kadi M, Erdem T, Senel K. The relationship between serum prolactin levels and disease activity in patients with Behcet's disease. Cell Biochem Funct. 2006;24:353–6.

Babey M, Sahli R, Vajtai I, Andres RH, Seiler RW. Pituitary surgery for small prolactinomas as an alternative to treatment with dopamine agonists. Pituitary. 2011;14:222–30.

Balbach L, Wallaschofski H, Völzke H, Nauck M, Dörr M, Haring R. Serum prolactin concentrations as risk factor of metabolic syndrome or type 2 diabetes? BMC Endocr Disord. 2013;13:12–9.

Barber TM, Kenkre J, Garnett C, Scott RV, Byrne JV, Wass JA. Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma. Clin Endocrinol. 2011;75:819–24.

Bart G, Borg L, Schluger JH, Green M, Ho A, Kreek MJ. Suppressed prolactin response to dynorphin A1-13 in methadone-maintained versus control subjects. J Pharmacol Exp Ther. 2003;306:581–7.

Beer TM, Bland LB, Bussiere JR, Neiss MB, Wersinger EM, Garzotto M, Ryan CW, Janowsky JS. Testosterone loss and estradiol administration modify memory in men. J Urol. 2006;175:130–5.

Behan LA, Draman MS, Moran C, King T, Crowley RK, O'Sullivan EP, Smith D, Thompson CJ, Agha A. Secondary resistance to cabergoline therapy in a macroprolactinoma: a case report and literature review. Pituitary. 2011;14:362–6.

Bellantuono C, Santone G. Efficacy, tolerability and safety of paliperidone extended-release in the treatment of schizophrenia and schizoaffective disorder. Riv Psichiatr. 2012;47:5–20.

Ben-Jonathan N, Mershon JL, Allen DL, Steinmetz RW. Extrapituitary prolactin: distribution, regulation, functions, and clinical aspects. Endocr Rev. 1996;17:639–69.

Ben-Jonathan N, Hugo ER, Brandebourg TD, LaPensee CR. Focus on prolactin as a metabolic hormone. Trends Endocrinol Metab. 2006;17:110–6.

Berchtold S, Volarevic S, Moriggl R, Mercep M, Groner B. Dominant negative variants of the SHP-2 tyrosine phosphatase inhibit prolactin activation of Jak2 (janus kinase 2) and induction of

Stat5 (signal transducer and activator of transcription 5)-dependent transcription. Mol Endocrinol. 1998;12:556–67.

Berinder K, Akre O, Granath F, Hulting AL. Cancer risk in hyperprolactinemia patients: a population-based cohort study. Eur J Endocrinol. 2011;165:209–15.

Besnard I, Auclair V, Callery G, Gabriel-Bordenave C, Roberge C. Antipsychotic-drug-induced hyperprolactinemia: physiopathology, clinical features and guidance. Encéphale. 2014;40:86–94.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536–59.

Biswas M, Smith J, Jadon D, McEwan P, Rees DA, Evans LM, Scanlon MF, Davies JS. Long-term remission following withdrawal of dopamine agonist therapy in subjects with microprolactinomas. Clin Endocrinol. 2005;63:26–31.

Bogazzi F, Buralli S, Manetti L, Raffaelli V, Cigni T, Lombardi M, Boresi F, Taddei S, Salvetti A, Martino E. Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia. Int J Clin Pract. 2008;62:1864–9.

Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr Rev. 1998;19:225–68.

Bonert VS, Melmed S (2006) Acromegaly with moderate hyperprolactinemia caused by an intrasellar macroadenoma. Nat Clin Pract Endocrinol Metab 2: 408-12

Brandebourg T, Hugo E, Ben-Jonathan N. Adipocyte prolactin: regulation of release and putative functions. Diabetes Obes Metab. 2007;9:464–76.

Brelje TC, Stout LE, Bhagroo NV, Sorenson RL. Distinctive roles for prolactin and growth hormone in the activation of signal transducer and activator of transcription 5 in pancreatic islets of langerhans. Endocrinology. 2004;145:4162–75.

Brown RS, Herbison AE, Grattan DR. Prolactin regulation of kisspeptin neurones in the mouse brain and its role in the lactation-induced suppression of kisspeptin expression. J Neuroendocrinol. 2014;26:898–908.

Buchfelder M, Schlaffer S. Surgical treatment of pituitary tumours. Best Pract Res Clin Endocrinol Metab. 2009;23:677–92.

Buvat J, Shabsigh R, Guay A, Gooren L, Torres LO, Meuleman E. Hormones, metabolism, aging, and men's health. In: Montorsi F, Basson R, Adaikan G, Becher E, Clayton A, Giuliano F, et al., editors. Standard practice in sexual medicine. Oxford: Blackwell Publishing; 2006. p. 225–86.

Byerly M, Suppes T, Tran QV, Baker RA. Clinical implications of antipsychotic-induced hyperprolactinemia in patients with schizophrenia spectrum or bipolar spectrum disorders: recent developments and current perspectives. J Clin Psychopharmacol. 2007;27:639–61.

Caccavelli L, Feron F, Morange I, Rouer E, Benarous R, Dewailly D, Jaquet P, Kordon C, Enjalbert A. Decreased expression of the two D2 dopamine receptor isoforms in bromocriptine-resistant prolactinomas. Neuroendocrinology. 1994;60:314–22.

Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Law E, Marek J, Scanlon M, Sobrinho LG, Wass JAH. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006;65:265–73.

Castinetti F, Nagai M, Morange I, Dufour H, Caron P, Chanson P, Cortet-Rudelli C, Kuhn JM, Conte-Devolx B, Regis J, Brue T. Long-term results of stereotactic radiosurgery in secretory pituitary adenomas. J Clin Endocrinol Metab. 2009;94:3400–7.

Cavallaro R, Cocchi F, Angelone SM, Lattuada E, Smeraldi E. Cabergoline treatment of risperidone-induced hyperprolactinemia: a pilot study. J Clin Psychiatry. 2004;65:187–90.

Chandrashekar V, Bartke A. Influence of endogenous prolactin on the luteinizing hormone stimulation of testicular steroidogenesis and the role of prolactin in adult male rats. Steroids. 1988;51:559–76.

Chavez-Rueda K, Hernandez J, Zenteno E, Leanos-Miranda A, Legorreta-Haquet MV, Blanco-Favela F. Identification of prolactin as a novel immunomodulator on the expression of co-stimulatory molecules and cytokine secretions on T and B human lymphocytes. Clin Immunol. 2005;116:182–91.

Chwieduk CM, Keating GM. Paliperidone extended release: a review of its use in the management of schizophrenia. Drugs. 2010;70:1295–317.

Clevenger CV, Furth PA, Hankinson SE, Schuler LA. The role of prolactin in mammary carcinoma. Endocr Rev. 2003;24:1–27.

Cohen LG, Biederman J. Treatment of risperidone-induced hyperprolactinemia with a dopamine agonist in children. J Child Adolesc Psychopharmacol. 2001;11:435–40.

Cohen-Inbar O, Xu Z, Schlesinger D, Vance ML, Sheehan JP. Gamma knife radiosurgery for medically and surgically refractory prolactinomas: long-term results. Pituitary. 2015;18:820–30.

Colao A. Pituitary tumours: the prolactinoma. Best Pract Res Clin Endocrinol Metab. 2009;23:575–96.

Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B, Annunziato L, Lombardi G. Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. J Clin Endocrinol Metab. 1997;82:876–83.

Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med. 2003;349:2023–33.

Colao A, Galderisi M, Di Sarno A, Pardo M, Gaccione M, D'Andrea M, Guerra E, Pivonello R, Lerro G, Lombardi G. Increased prevalence of tricuspid regurgitation in patients with prolactinomas chronically treated with cabergoline. J Clin Endocrinol Metab. 2008;93:3777–84.

Cookson J. Oestrogens, dopamine and mood. Br J Psychiatry. 1981;139:365–6.

Corona G, Mannucci E, Fisher AD, Lotti F, Ricca V, Balercia G, Petrone L, Forti G, Maggi M. Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. J Sex Med. 2007;4:1485–93.

Cosman D, Lyman SD, Idzerda RL, Beckmann MP, Park LS, Goodwin RG, March CJ. A new cytokine receptor superfamily. Trends Biochem Sci. 1990;15:265–70.

Couldwell WT, Weiss MH. Medical and surgical management of microprolactinoma. Pituitary. 2004;7:31–2.

Craig MC, Fletcher PC, Daly EM, Rymer J, Cutter WJ, Brammer M, Giampietro V, Wickham H, Maki PM, Murphy DG. Gonadotropin hormone releasing hormone agonists alter prefrontal function during verbal encoding in young women. Psychoneuroendocrinology. 2007;32:1116–27.

Craig MC, Fletcher PC, Daly EM, Picchioni MM, Brammer M, Giampietro V, Rymer J, McGuire PK, Maki PM, Murphy DG. A study of visuospatial working memory pre- and post-Gonadotropin Hormone Releasing Hormone agonists (GnRHa) in young women. Horm Behav. 2008;54:47–59.

Crambert S, Sjoberg A, Eklof AC, Ibarra F, Holtback U. Prolactin and dopamine 1-like receptor interaction in renal proximal tubular cells. Am J Phys. 2010;299:F49–54.

Creemers LB, Zelissen PM, van't Verlaat JW, Koppeschaar HP. Prolactinoma and body weight: a retrospective study. Acta Endocrinol. 1991;125:392–6.

Cruz N, Vieta E. Asenapine: a new focus on the treatment of mania. Rev Psiquiatr Salud Ment. 2011;4:101–8.

Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab. 2006;91:4769–75.

Das R, Vonderhaar BK. Prolactin as a mitogen in mammary cells. J Mammary Gland Biol Neoplasia. 1997;2:29–39.

De Bellis A, Bizzarro A, Pivonello R, Lombardi G, Bellastella A. Prolactin and autoimmunity. Pituitary. 2005;8:25–30.

Dekkers OM, Lagro J, BurmanP JJO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab. 2010a;95:43–51.

Dekkers OM, Romijn JA, de Boer A, Vandenbroucke JP. The risk for breast cancer is not evidently increased in women with hyperprolactinemia. Pituitary. 2010b;13:195–8.

Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J. Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. J Clin Endocrinol Metab. 1997;82:2102–7.

Delgrange E, Donckier J, Maiter D. Hyperprolactinaemia as a reversible cause of weight gain in male patients? Clin Endocrinol. 1999;50:271.

Delgrange E, Daems T, Verhelst J, Abs R, Maiter D. Characterization of resistance to the prolactin-lowering effects of cabergoline in macroprolactinomas: a study in 122 patients. Eur J Endocrinol. 2009;160:747–52.

Demura R, Ono M, Demura H, Shizume K, Oouchi H. Prolactin directly inhibits basal as well as gonadotropin-stimulated secretion of progesterone and 17b-estradiol in the human ovary. J Clin Endocrinol Metab. 1982;54:1246–50.

Doknic M, Pekic S, Zarkovic M, Medic-Stojanoska M, Dieguez C, Casanueva F, Popovic V. Dopaminergic tone and obesity: an insight from prolactinomas treated with bromocriptine. Eur J Endocrinol. 2002;147:77–84.

Dombrowicz D, Sente B, Closset J, Hennen G. Dose-dependent effects of human prolactin on the immature hypophysectomized rat testis. Endocrinology. 1992;130:695–700.

Dorrington JH, Gore-Langton RE. Antigonadal action of prolactin: further studies on the mechanism of inhibition of follicle-stimulating hormone-induced aromatase activity in rat granulosa cell cultures. Endocrinology. 1982;110:1701–7.

Drago F, Pellegrini-Quarantotti B, Scapagnini U, Gessa GL. Short-term endogenous hyperprolactinemia and sexual behaviour of me rats. Physiol Behav. 1981;26:277–9.

Erem C, Kocak M, Nuhoglu I, Yilmaz M, Ucuncu O. Blood coagulation, fibrinolysis and lipid profile in patients with prolactinoma. Clin Endocrinol. 2010;73:502–27.

Ernst B, Thurnheer M, Schultes B. Basal serum prolactin levels in obesity-unrelated to parameters of the metabolic syndrome and unchanged after massive weight loss. Obes Surg. 2009;19:1159–62.

Faupel-Badger JM, Duggan MA, Sherman ME, Garcia-Closas M, Yang XR, Lissowska J, Brinton LA, Peplonska B, Vonderhaar BK, Figueroa JD. Prolactin receptor expression and breast cancer: relationships with tumor characteristics among pre- and post-menopausal women in a population-based case-control study from Poland. Horm Cancer. 2014;5:42–50.

Fava M, Fava GA, Kellner R, Buckman MT, Lisansky J, Serafini E, DeBesi L, Mastrogiacomo I. Psychosomatic aspects of hyperprolactinemia. Psychother Psychosom. 1983;40:257–62.

Feldman M, Ruan W, Cunningham BC, Wells JA, Kleinberg DL. Evidence that the growth hormone receptor mediates differentiation and development of the mammary gland. Endocrinology. 1993;133:1602–8.

Feltus FA, Groner B, Melner MH. Stat5-mediated regulation of the human type II 3b-hydroxysteroid dehydrogenase/delta5-delta4 isomerase gene: activation by prolactin. Mol Endocrinol. 1999;13:1084–93.

Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol. 2010;72:377–82.

Frantz AG. Prolactin. N Engl J Med. 1978;298:201–7.

Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function and regulation of secretion. Physiol Rev. 2000;80:1523–631.

Freemark M, Avril I, Fleenor D, Driscoll P, Petro A, Opara E, Kendall W, Oden J, Bridges S, Binart N, Breant B, Kelly PA. Targeted deletion of the PRL receptor: effects on islet development, insulin production, and glucose tolerance. Endocrinology. 2002;143:1378–85.

Friedrich N, Schneider HJ, Spielhagen C, Markus MR, Haring R, Grabe HJ, Buchfelder M, Wallaschofski H, Nauck M. The association of serum prolactin concentration with inflammatory

biomarkers – cross-sectional findings from the population-based Study of Health in Pomerania. Clin Endocrinol. 2011;75:561–6.
Fuh G, Wells JA. Prolactin receptor antagonists that inhibit the growth of breast cancer cell lines. J Biol Chem. 1995;270:13133–7.
Georgiopoulos GA, Stamatelopoulos KS, Lambrinoudaki I, Lykka M, Kyrkou K, Rizos D, Creatsa M, Christodoulakos G, Alevizaki M, Sfikakis PP, Papamichael C. Prolactin and preclinical atherosclerosis in menopausal women with cardiovascular risk factors. Hypertension. 2009;54:98–105.
Gettler LT, McDade TW, Feranil AB, Kuzawa CW. Prolactin, fatherhood, and reproductive behavior in human males. Am J Phys Anthropol. 2012;148:362–70.
Gibney J, Smith TP, McKenna TJ. The impact on clinical practice of routine screening for macroprolactin. J Clin Endocrinol Metab. 2005;90:3927–32.
Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27:485–534.
Glass MR, Shaw RW, Butt WR, Edwards RL, London DR. An abnormality of oestrogen feedback in amenorrhoea–galactorrhoea. Br Med J. 1975;3:274–5.
Goffin V, Kelly PA. The prolactin/growth hormone receptor family: structure/function relationships. J Mammary Gland Biol Neoplasia. 1997;2:7–17.
Goffin V, Shiverick KT, Kelly PA, Martial JA. Sequence function relationships within the expanding family of prolactin, growth hormone, placental lactogen and related proteins in mammals. Endocr Rev. 1996;17:385–410.
Goffin V, Bernichtein S, Touraine P, Kelly P. Development and potential clinical uses of human prolactin receptor antagonists. Endocr Rev. 2005;26:400–22.
Goldhar AS, Vonderhaar BK, Trott JF, Hovey RC. Prolactin induced expression of vascular endothelial growth factor via Egr-1. Mol Cell Endocrinol. 2005;232:9–19.
Green AI, Brown WA. Prolactin and neuroleptic drugs. Endocrinol Metab Clin N Am. 1988;17:213–23.
Greenspan SL, Neer RM, Ridgway EC, Klibanski A. Osteoporosis in men with hyperprolactinemic hypogonadism. Ann Intern Med. 1986;104:777–82.
Greenspan SL, Oppenheim DS, Klibanski A. Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. Ann Intern Med. 1989;110:526–31.
Grigorova M, Sherwin BB, Tulandi T. Effects of treatment with leuprolide acetate depot on working memory and executive functions in young premenopausal women. Psychoneuroendocrinology. 2006;31:935–47.
Gunasekar PG, Kumaran B, Govindarajulu P. Prolactin and leydig cell steroidogenic enzymes in the bonnet monkey (macaca radiata). Int J Androl. 1988;11:53–9.
Gunasekar PG, Kumaran B, Govindarajulu P. Role of prolactin on leydig, sertoli and germ cellular neutral lipids in bonnet monkeys, macaca radiata. Endocrinologia Japonica. 1991;38:1–8.
Hair WM, Gubbay O, Jabbour HN, Lincoln GA. Prolactin receptor expression in human testis and accessory tissues: localization and function. Mol Hum Reprod. 2002;8:606–11.
Hamosh M, Hamosh P. The effect of prolactin on the lecithin content of fetal rabbit lung. J Clin Invest. 1977;59:1002–5.
Hankinson SE, Willett WC, Michaud DS, Manson JE, Colditz GA, Longcope C, Rosner B, Speizer FE. Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 1999;91:629–34.
Harvey PW, Everett DJ, Springall CJ. Hyperprolactinaemia as an adverse effect in regulatory and clinical toxicology: role in breast and prostate cancer. Hum Exp Toxicol. 2006;25:395–404.
Harvey PW, Everett DJ, Springall CJ. Adverse effects of prolactin in rodents and humans: breast and prostate cancer. J Psychopharmacol. 2008;22:20–7.
Henry JF, Sherwin BB. Hormones and cognitive functioning during late pregnancy and postpartum: a longitudinal study. Behav Neurosci. 2012;126:73–85.
Herring N, Szmigielski C, Becher H, Karavitaki N, Wass JA. Valvular heart disease and the use of cabergoline for the treatment of prolactinoma. Clin Endocrinol. 2009;70:104–8.

Honbo KS, van Herle AJ, Kellett KA. Serum prolactin levels in untreated primary hypothyroidism. Am J Med. 1978;64:782–7.

Horseman ND, Zhao W, Montecino-Rodriguez E, Tanaka M, Nakashima K, Engle SJ, Smith F, Markoff E, Dorshkind K. Defective mammopoiesis, but normal hematopoiesis, in mice with a targeted disruption of the prolactin gene. EMBO J. 1997;16:6926–35.

Hou SH, Grossman S, Molitch ME. Hyperprolactinemia in patients with renal insufficiency and chronic renal failure requiring hemodialysis or chronic ambulatory peritoneal dialysis. Am J Kidney Dis. 1985;6:245–9.

Huang KE, Bonfiglio TA, Muechler EK. Transient hyperprolactinemia in infertile women with luteal phase deficiency. Obstet Gynecol. 1991;78:651–5.

Hurel SJ, Harris PE, McNicol AM, Foster S, Kelly WF, Baylis PH. Metastatic prolactinoma: effect of octreotide, cabergoline, carbo-platin and etoposide; immunocytochemical analysis of proto-oncogene expression. J Clin Endocrinol Metab. 1997;82:2962–5.

Ibarra F, Crambert S, Eklof AC, Lundquist A, Hansell P, Holtback U. Prolactin, a natriuretic hormone, interacting with renal dopamine system. Kidney Int. 2005;68:1700–7.

Ignacak A, Kasztelnik M, Sliwa T, Korbut R, Rajda K, Guzik T. Prolactin not only lactotrophin. A "new" view of the "old" hormone. J Physiol Pharmacol. 2012;63:435–43.

Ikeda H, Watanabe K, Tominaga T, Yoshimoto T. Transsphenoidal microsurgical results of female patients with prolactinomas. Clin Neurol Neurosurg. 2013;115:1621–5.

Ishida M, Yoshida M, Fukuta S, Uemura K, Iijima M, Horiguchi K, Harigaya T. Analysis of prolactin gene expression and cleaved prolactin variants in the mouse testis and spermatozoa. J Reprod Dev. 2010;56:567–74.

Jabbour HN, Lincoln GA. Prolactin receptor expression in the testis of the ram: localisation, functional activation and the influence of gonadotrophins. Mol Cell Endocrinol. 1999;148:151–61.

Janicak PG, Winans EA. Paliperidone ER: a review of the clinical trial data. Neuropsychiatr Dis Treat. 2007;3:869–97.

Jeffcoate WJ, Pound N, Sturrock ND, Lambourne J. Long-term follow-up of patients with hyperprolactinaemia. Clin Endocrinol. 1996;45:299–303.

Jezkova J, Hana V, Krsek M, Weiss V, Vladyka V, Liscak R, Vymazal J, Pecen L, Marek J. Use of the Leksell gamma knife in the treatment of prolactinoma patients. Clin Endocrinol. 2009;70:732–41.

Karavitaki N, Thanabalasingham G, Shore HC, Trifanescu R, Ansorge O, Meston N, Turner HE, Wass JA. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. Clin Endocrinol. 2006;65:524–9.

Kars M, Delgado V, Holman ER, Feelders RA, Smit JW, Romijn JA, Bax JJ, Pereira AM. Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. J Clin Endocrinol Metab. 2008;93:3348–56.

Kars M, Souverein PC, Herings RM, Romijn JA, Vandenbroucke JP, de Boer A, Dekkers OM. Estimated age- and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia. J Clin Endocrinol Metab. 2009;94:2729–34.

Karunakaran S, Page RC, Wass JA. The effect of the menopause on prolactin levels in patients with hyperprolactinaemia. Clin Endocrinol. 2001;54:295–300.

Kato Y, Shimatsu A, Matsushita N, Ohta H, Imura H. Role of vasoactive intestinal polypeptide (VIP) in regulating the pituitary function in man. Peptides. 1984;5:389–94.

Kearns AE, Goff DC, Hayden DL, Daniels GH. Risperidone associated hyperprolactinemia. Endocr Pract. 2000;6:425–9.

Kelly PA, Djiane J, Postel-Vinay MC, Edery M. The prolactin/growth hormone receptor family. Endocr Rev. 1991;12:235–51.

Keye WR, Yuen BH, Knopf RF, Jaffe RB. Amenorrhea, hyperprolactinemia and pituitary enlargement secondary to primary hypothyroidism. Successful treatment with thyroid replacement. Obstet Gynecol. 1976;48:697–702.

Kharlip J, Salvatori R, Yenokyan G, Wand GS. Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. J Clin Endocrinol Metab. 2009;94:2428–36.

Kinon BJ, Gilmore JA, Liu H, Halbreich UM. Prevalence of hyperprolactinaemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology. 2003;28:55–68.

Kleinberg DL, Noel GL, Frantz AG. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. N Engl J Med Mar. 1977;296:589–600.

Klibanski A, Greenspan SL. Increase in bone mass after treatment of hyperprolactinemic amenorrhea. N Engl J Med. 1986;315:542–6.

Klibanski A, Neer RM, Beitins IZ, Ridgway EC, Zervas NT, McArthur JW. Decreased bone density in hyperprolactinemic women. N Engl J Med. 1980;303:1511–4.

Kokay IC, Petersen SL, Grattan DR. Identification of prolactin-sensitive GABA and kisspeptin neurons in regions of the rat hypothalamus involved in the control of fertility. Endocrinology. 2011;152:526–35.

Kong DS, Lee JI, Lim DH, Kim KW, Shin HJ, Nam DH, Park K, Kim JH. The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas: long-term results of 125 consecutive patients treated in a single institution. Cancer. 2007;110:854–60.

Kooy A, de Greef WJ, Vreeburg JT, Hackeng WH, Ooms MP, Lamberts SW, Weber RF. Evidence for the involvement of corticotropin-releasing factor in the inhibition of gonadotropin release induced by hyperprolactinemia. Neuroendocrinology. 1990;51:261–6.

Kovacs K, Stefaneanu L, Horvath E, Buchfelder M, Fahlbusch R, Becker W. Prolactin-producing pituitary tumor: resistance to dopamine agonist therapy. Case report. J Neurosurg. 1995;82:886–90.

Krasnow JS, Hickey GJ, Richards JS. Regulation of aromatase mRNA and estradiol biosynthesis in rat ovarian granulosa and luteal cells by prolactin. Mol Endocrinol. 1990;4:13–22.

Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M. Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. Eur J Endocrinol. 2008;158:11–8.

Kukstas LA, Domec C, Bascles L, Bonnet J, Verrier D, Israel JM, Vincent JD. Different expression of the two dopaminergic D2 receptors, D2415 and D2444, in two types of lactotroph each characterized by their response to dopamine, and modification of expression by sex steroids. Endocrinology. 1991;129:1101–3.

Lancellotti P, Livadariu E, Markov M, Daly AF, Burlacu MC, Betea D, Pierard L, Beckers A. Cabergoline and the risk of valvular lesions in endocrine disease. Eur J Endocrinol. 2008;159:1–5.

Lania AG, Ferrero S, Pivonello R, Mantovani G, Peverelli E, Di Sarno A, Beck-Peccoz P, Spada A, Colao A. Evolution of an aggressive prolactinoma into a growth hormone secreting pituitary tumor coincident with GNAS gene mutation. J Clin Endocrinol Metab. 2010;95:13–7.

Leanos-Miranda A, Cardenas-Mondragon G. Serum free prolactin concentrations in patients with systemic lupus erythematosus are associated with lupus activity. Rheumatology. 2006;45:97–101.

Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382:951–62.

Lim VS, Kathpalia SC, Frohman LA. Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: reversal after transplantation. J Clin Endocrinol Metab. 1979;48:101–7.

Lin Y, Hyde JF, Vore M. Prolactin regulates maternal bile secretory function post partum. J Pharmacol Exp Ther. 1992;261:560–6.

Ling C, Svensson L, Odén B, Weijdegård B, Edén B, Edén S, Billig H. Identification of functional prolactin (PRL) receptor gene expression: PRL inhibits lipoprotein lipase activity in human white adipose tissue. J Clin Endocrinol Metab. 2003;88:1804–8.

Lotti F, Corona G, Maseroli E, Rossi M, Silverii A, Degl'innocenti S, Rastrelli G, Forti G, Maggi M. Clinical implications of measuring prolactin levels in males of infertile couples. Andrology. 2013;1:764–71.

Lu ML, Shen WW, Chen CH. Time course of the changes in antipsychotic-induced hyperprolactinemia following the switch to aripiprazole. Prog Neuro-Psychopharmacol Biol Psychiatry. 2008;32:1978–81.
Luciano AA, Sherman BM, Chapler FK, Hauser KS, Wallace RB. Hyperprolactinemia and contraception: a prospective study. Obstet Gynecol. 1985;65:506–10.
Machida T, Taga M, Minaguchi H. Effect of prolactin (PRL) on lipoprotein lipase (LPL) activity in the rat fetal liver. Asia Oceania J Obstet Gynaecol. 1990;16:261–5.
Malaguarnera L, Pilastro MR, Quan S, Ghattas MH, Yang L, Mezentsev AV, Kushida T, Abraham NG, Kappas A. Significance of heme oxygenase in prolactin-mediated cell proliferation and angiogenesis in human endothelial cells. Int J Mol Med. 2002;10:433–40.
Mancini T, Casanueva FF, Giustina A. Hyperprolactinemia and prolactinomas. Endocrinol Metab Clin N Am. 2008;37:67–99.
Manjer J, Johansson R, Berglund G, Janzon L, Kaaks R, Agren A, Lenner P. Postmenopausal breast cancer risk in relation to sex steroid hormones, prolactin and SHBG (Sweden). Cancer Causes Control. 2003;14:599–607.
Matsuzaki T, Azuma K, Irahara M, Yasui T, Aono T. Mechanism of anovulation in hyperprolactinemic amenorrhea determined by pulsatile gonadotropin-releasing hormone injection combined with human chorionic gonadotropin. Fertil Steril. 1994;62:1143–9.
Mazziotti G, Porcelli T, Mormando M, De Menis E, Bianchi A, Mejia C, Mancini T, De Marinis L, Giustina A. Vertebral fractures in males with prolactinoma. Endocrine. 2011;39:288–93.
McNatty KP. Relationship between plasma prolactin and the endocrine microenvironment of the developing human antral follicle. Fertil Steril. 1979;32:433–8.
Melmed S, Kleinberg D. Anterior pituitary. In: Larsen P, Kronenberg H, Melmed S, Polonsky K, editors. Williams textbook of endocrinology. 10th ed. Philadelphia: Saunders; 2003. p. 177–279.
Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:273–88.
Meltzer HY, Fang VS. Serum prolactin levels in schizophrenia-effect of antipsychotic drugs: a preliminary report. In: Sachar EJ, editor. Hormones, behavior, and psychopathology. New York: Raven Press; 1976.
Mendelson JH, Mello NK, Teoh SK, Ellingboe J, Cochin J. Cocaine effects on pulsatile secretion of anterior pituitary, gonadal, and adrenal hormones. J Clin Endocrinol Metab. 1989;69:1256–60.
Mingrone G, Manco M, Iaconelli A, Gniuli D, Bracaglia R, Leccesi L, Calvani M, Nolfe G, Basu S, Berria R. Prolactin and insulin ultradian secretion and adipose tissue lipoprotein lipase expression in severely obese women after bariatric surgery. Obesity (Silver Spring). 2008;16:1831–7.
Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab. 2002;87:5001–7.
Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, Resnick SM. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004;27(62):188–93.
Molinari C, Grossini E, Mary DA, Uberti F, Ghigo E, Ribichini F, Surico N, Vacca G. Prolactin induces regional vasoconstriction through the beta2-adrenergic and nitric oxide mechanisms. Endocrinology. 2007;148:4080–90.
Molitch ME. Pathologic hyperprolactinemia. Endocrinol Metab Clin N Am. 1992;21:877–901.
Molitch ME. Prolactinoma. In: Melmed S, editor. Pituitary. Cambridge: Blackwell Science; 1995. p. 433–77.
Molitch ME. Dopamine resistance of prolactinomas. Pituitary. 2003;6:19–27.
Molitch ME. Medication-induced hyperprolactinemia. Mayo Clin Proc. 2005a;80:1050–7.
Molitch ME. Pharmacologic resistance in prolactinoma patients. Pituitary. 2005b;8:43–52.
Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. Eur J Endocrinol. 2015;172:R205–13.
Molitch ME, Reichlin S. Hyperprolactinemic disorders. Dis Mon. 1982;28:1–58.

Molitch ME, Elton RL, Blackwell RE, Caldwell B, Chang RJ, Jaffe R, Joplin G, Robbins RJ, Tyson J, Thorner MO. Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. J Clin Endocrinol Metab. 1985;60:698–705.

Montejo AL. Prolactin awareness: an essential consideration for physical health in schizophrenia. Eur Neuropsychopharmacol. 2008;18:101–30.

Montejo AL, Rico-Villademoros F, Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Changes in sexual function for outpatients with schizophrenia or other psychotic disorders treated with ziprasidone in clinical practice settings: a 3-month prospective, observational study. J Clin Psychopharmacol. 2008;28:568–70.

Montes de Oca P, Macotela Y, Nava G, López-Barrera F, de la Escalera GM, Clapp C. Prolactin stimulates integrin-mediated adhesion of circulating mononuclear cells to endothelial cells. Lab Investig. 2005;85:633–42.

Morange I, Barlier A, Pellegrini I, Brue T, Enjalbert A, Jaquet P. Prolactinomas resistant to bromocriptine: long-term efficacy of quinagolide and outcome of pregnancy. Eur J Endocrinol. 1996;135:413–20.

Morley JE, Dawson M, Hodgkinson H, Kalk WJ. Galactorrhea and hyperprolactinemia associated with chest wall injury. J Clin Endocrinol Metab. 1977;45:931–5.

Nevalainen MT, Valve EM, Ahonen T, Yagi A, Paranko J, Härkönen PL. Androgen-dependent expression of prolactin in rat prostate epithelium in vivo and in organ culture. FASEB J. 1997a;11:1297–307.

Nevalainen MT, Valve EM, Ingleton PM, Nurmi M, Martikainen PM, Harkonen PL. Prolactin and prolactin receptors are expressed and functioning in human prostate. J Clin Invest. 1997b;99:618–27.

Newey PJ, Gorvin CM, Cleland SJ, Willberg CB, Bridge M, Azharuddin M, Drummond RS, van der Merwe PA, Klenerman P, Bountra C, Thakker RV. Mutant prolactin receptor and familial hyperprolactinemia. N Engl J Med. 2013;369:2012–20.

Nicol M, Willis C, Yiangou C, Sinnett D, Shousha S. Relationship between serum prolactin levels and histology of benign and malignant breast lesions: a detailed study of 153 consecutive cases. Breast J. 2002;8:281–5.

Nicoll C. Ontogeny and evolution of prolactins' function. Fed Proc. 1980;39:2563–6.

Nilsson L, Binart N, Bohlooly-Y M, Bramnert M, Egecioglu E, Kindblom J, Kelly PA, Kopchick JJ, Ormandy CJ, Ling C, Billig H (2005) Prolactin and growth hormone regulate adiponectin secretion and receptor expression in adipose tissue. Biochem Biophys Res Commun 331: 1120-1126

Nomikos P, Buchfelder M, Fahlbusch R. Current management of prolactinomas. J Neuro-Oncol. 2001;54:139–50.

Oh MC, Aghi MK. Dopamine agonist-resistant prolactinomas. J Neurosurg. 2011;114:1369–79.

Oliveira MC, Pizarro CB, Golbert L, Micheletto C. Hyperprolactinemia and psychological disturbance. Arq Neuropsiquiatr. 2000;58:671–6.

Orbach H, Shoenfeld Y. Hyperprolactinemia and autoimmune diseases. Autoimmun Rev. 2007;6:537–42.

Pan L, Zhang N, Wang EM, Wang BJ, Dai JZ, Cai PW. Gamma knife radiosurgery as a primary treatment for prolactinomas. J Neurosurg. 2000;93:10–3.

Pellegrini I, Rasolonjanahary R, Gunz G, Bertrand P, Delivet S, Jedynak CP, Kordon C, Peillon F, Jaquet P, Enjalbert A. Resistance to bromocriptine in prolactinomas. J Clin Endocrinol Metab. 1989;69:500–9.

Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology. 1992;17:485–95.

Pinsky M, Hellstrom W. Hypogonadism, ADAM, and hormone replacement. Ther Adv Urol. 2010;2:99–104.

Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klibanski A. Primary medical therapy of micro- and macroprolactinomas in men. J Clin Endocrinol Metab. 2000;85:3053–7.

Pippard C, Baylis PH. Prolactin stimulates Na+-K+-ATPase activity located in the outer renal medulla of the rat. J Endocrinol. 1986;108:95–9.

Pollock A, McLaren EH. Serum prolactin concentration in patients taking neuroleptic drugs. Clin Endocrinol. 1998;49:513–6.

Postel-Vinay MC, Belair L, Kayser C, Kelly PA, Djiane J. Identification of prolactin and growth hormone binding proteins in milk. Proc Natl Acad Sci U S A. 1991;188:6687–90.

Poyraz BC, Aksoy C, Balcioglu I. Increased incidence of autoimmune thyroiditis in patients with antipsychotic-induced hyperprolactinemia. Eur Neuropsychopharmacol. 2008;18:667–72.

Prabhakar VK, Davis JR. Hyperprolactinemia. Best Pract Res Clin Obstet Gynaecol. 2008;22:341–53.

Pujianto DA, Curry BJ, Aitken RJ. Prolactin exerts a prosurvival effect on human spermatozoa via mechanisms that involve the stimulation of Akt phosphorylation and suppression of caspase activation and capacitation. Endocrinology. 2010;151:1269–79.

Ramasharma K, Li CH. Human pituitary and placental hormones control human insulin-like growth factor II secretion in human granulosa cells. Proc Natl Acad Sci U S A. 1987;84:2643–7.

Ravault JP, Courot M, Garnier D, Pelletier J, Terqui M. Effect of 2-bromo-α-ergocryptine (CB154) on plasma prolactin, LH and testosterone levels, accessory reproductive glands and spermatogenesis in lambs during puberty. Biol Reprod. 1977;17:192–7.

Reavley A, Fisher AD, Owen D, Creed FH, Davis JR. Psychological distress in patients with hyperprolactinaemia. Clin Endocrinol. 1997;47:343–8.

Ress C, Maeser PA, Tschoner A, Loacker L, Salzmann K, Staudacher G, Melmer A, Zoller H, Vogel W, Griesmacher A, Tilg H, Graziadei I, Kaser S. Serum prolactin in advanced chronic liver disease. Horm Metab Res. 2014;46:800–3.

Reuwer AQ, Twickler MT, Hutten BA, Molema FW, Wareham NJ, Dallinga-Thie GM, Bogorad RL, Goffin V, Smink-Bol M, Kastelein JJ, Boekholdt SM, Khaw KT. Prolactin levels and the risk of future coronary artery disease in apparently healthy men and women. Circ Cardiovasc Genet. 2009;2:389–95.

Reuwer AQ, van Eijk M, Houttuijn-Bloemendaal FM, van der Loos CM, Claessen N, Teeling P, Kastelein JJ, Hamann J, Goffin V, von der Thüsen JH, Twickler MT, Aten J. The prolactin receptor is expressed in macrophages within human carotid atherosclerotic plaques: a role for prolactin in atherogenesis? J Endocrinol. 2011;208:107–17.

Richardsson BP. Evidence for a physiological role of prolactin in osmoregulation in the rat after its inhibition by 2-bromo-α-ergokryptine. Br J Pharmacol. 1973;47:623–4.

Rickenlund A, Thoren M, Carlstrom K, von Schoultz B, Hirschberg AL. Diurnal profiles of testosterone and pituitary hormones suggest different mechanisms for menstrual disturbances in endurance athletes. J Clin Endocrinol Metab. 2004;89:702–7.

Rohmer V, Freneau E, Morange I, Simonetta C. Efficacy of quinagolide in resistance to dopamine agonists: results of a multi-center study. Club de l'Hypophyse. Ann Endocrinol (Paris). 2000;61:411–7.

Rubin RT, Poland RE, Tower BB. Prolactin-related testosterone secretion in normal adult men. J Clin Endocrinol Metab. 1976;42:112–6.

Saitis M, Papazisis G, Katsigiannopoulos K, Kouvelas D. Aripiprazole resolves amisulpride and ziprasidone-induced hyperprolactinemia. Psychiatry Clin Neurosci. 2008;62:624.

Samson SL, Hamrahian AH, Ezzat S, AACE Neuroendocrine and Pituitary Scientific Committee, American College of Endocrinology (ACE). American association of clinical endocrinologists, American college of endocrinology disease state clinical review: clinical relevance of macroprolactin in the absence or presence of true hyperprolactinemia. Endocr Pract. 2015;21:1427–35.

Sauder SE, Frager M, Case GD, Kelch RP, Marshall JC. Abnormal patterns of pulsatile luteinizing hormone secretion in women with hyperprolactinemia and amenorrhea: responses to bromocriptine. J Clin Endocrinol Metab. 1984;59:941–8.

Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. N Engl J Med. 2007;356:29–38.

Schlechte JA. Clinical practice. Prolactinoma. N Engl J Med. 2003;349:2035–41.

Schlechte JA, Sherman BM, Chapler FK, VanGilder J. Long-term follow-up of women with surgically treated prolactin-secreting pituitary tumours. J Clin Endocrinol Metab. 1986;62:1296–301.

Schlechte J, El-Khoury G, Kathol M, Walkner L. Forearm and vertebral bone mineral in treated and untreated hyperprolactinemic amenorrhea. J Clin Endocrinol Metab. 1987;64:1021–6.
Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: a prospective analysis. J Clin Endocrinol Metab. 1989;68:412–8.
Seppala M, Ranta T, Hirvonen E. Hyperprolactinaemia and luteal insufficiency. Lancet. 1976;1:229–30.
Seriwatanachai D, Krishnamra N, van Leeuwen JP. Evidence for direct effects of prolactin on human osteoblasts: inhibition of cell growth and mineralization. J Cell Biochem. 2009;107:677–85.
Serri O, Li L, Mamputu JC, Beauchamp MC, Maingrette F, Renier G. The influences of hyperprolactinemia and obesity on cardiovascular risk markers: effects of cabergoline therapy. Clin Endocrinol. 2006;64:366–70.
Shelly S, Boaz M, Orbach H. Prolactin and autoimmunity. Autoimmun Rev. 2012;11:A465–70.
Shibli-Rahhal A, Schlechte J. The effects of hyperprolactinemia on bone and fat. Pituitary. 2009;12:96–104.
Sievertsen GD, Lim VS, Nakawatase C, Frohman LA. Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. J Clin Endocrinol Metab. 1980;50:846–52.
Skrabanek P, McDonald D, de Valera E, Lanigan O, Powell D. Plasma prolactin in amenorrhoea, infertility, and other disorders: a retrospective study of 608 patients. Ir J Med Sci. 1980;149:236–45.
Sluijmer AV, Lappöhn RE. Clinical history and outcome of 59 patients with idiopathic hyperprolactinemia. Fertil Steril. 1992;58:72–7.
Smith S. Neuroleptic-associated hyperprolactinemia. Can it be treated with bromocriptine? J Reprod Med. 1992;37:737–40.
Smith S. The impact of hyperprolactinaemia on sexual function in patients with psychosis. J Psychopharmacol. 2008;22:63–9.
Smith TP, Suliman AM, Fahie-Wilson MN, McKenna TJ. Gross variability in the detection of prolactin in sera containing big big prolactin (macroprolactin) by commercial immunoassays. J Clin Endocrinol Metab. 2002a;87:5410–5.
Smith S, Wheeler MJ, Murray R, O'Keane V. The effects of antipsychotic-induced hyperprolactinaemia on the hypothalamic-pituitary-gonadal axis. J Clin Psychopharmacol. 2002b;22:109–14.
Sobrinho LG. Familial prolactinoma. Clin Endocrinol. 1995;43:511.
Sobrinho LG. Emotional aspects of hyperprolactinemia. Psychother Psychosom. 1998;67:133–9.
Sonigo C, Bouilly J, Carré N, Tolle V, Caraty A, Tello J, Simony-Conesa FJ, Millar R, Young J, Binart N. Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. J Clin Invest. 2012;122:3791–5.
Sorenson RL, Brelie TC, Hegie OD, Marshall S, Anaya P, Sheridam JD. Prolactin (in vitro) decreases the glucose stimulation threshold, enhances insulin secretion, and increases dye coupling among islet b cells. Endocrinology. 1987;121:1447–53.
Spitzer M, Sajjad R, Benjamin F. Pattern of development of hyperprolactinemia after initiation of haloperidol therapy. Obstet Gynecol. 1998;91:693–5.
St-Jean E, Blain F, Comtois R. High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. Clin Endocrinol. 1996;44:305–9.
Svestka J, Synek O, Tomanová J, Rodáková I, Cejpková A. Differences in the effect of second-generation antipsychotics on prolactinaemia: six weeks open-label trial in female in-patients. Neuro Endocrinol Lett. 2007;28:881–8.
Szosland K, Stasiak M, Lewiński A. Hyperprolactinemia diagnostics-dilemmas over optimal selection of prolactinemia time points. Ann Agric Environ Med. 2015;22:332–7.
Takase M, Tsutsui K, Kawashima S. Effects of prolactin and bromocryptine on the regulation of testicular luteinizing hormone receptors in mice. J Exp Zool. 1990;256:200–9.
Takeyama M, Nagareda T, Takatsuka D, Namiki M, Koizumi K, Aono T, Matsumoto K. Stimulatory effect of prolactin on luteinizing hormone-induced testicular 5 alpha-reductase activity in hypophysectomized adult rats. Endocrinology. 1986;118:2268–75.

Tolis G, Hickey J, Guyda H. Effects of morphine on serum growth hormone, cortisol, prolactin and thyroid stimulating hormone in man. J Clin Endocrinol Metab. 1975;41:797–800.

Tollin SR. Use of the dopamine agonists bromocriptine and cabergoline in the management of risperidone-induced hyperprolactinemia in patients with psychotic disorders. J Endocrinol Investig. 2000;23:765–70.

Unnikrishnan AG, Rajaratnam S, Seshadri MS, Kanagasapabathy AS, Stephen DC. The "hook effect" on serum prolactin estimation in a patient with macroprolactinoma. Neurol India. 2001;49:78–80.

Vallette S, Serri K, Rivera J, Santagata P, Delorme S, Garfield N, Kahtani N, Beauregard H, Aris-Jilwan N, Houde G, Serri O. Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. Pituitary. 2009;12:153–7.

Vera-Lastra O, Jara LJ, Espinoza LR. Prolactin and autoimmunity. Autoimmun Rev. 2002;1:360–4.

Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, Mahler C, Stevenaert A, Verlooy J, Raftopoulos C, Beckers A. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab. 1999;84:2518–22.

Volavka J, Czobor P, Cooper TB, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Lieberman JA. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychiatry. 2004;65:57–61.

Vroonen L, Jaffrain-Rea ML, Petrossians P, Tamagno G, Chanson P, Vilar L, Borson-Chazot F, Naves LA, Brue T, Gatta B, Delemer B, Ciccarelli E, Beck-Peccoz P, Caron P, Daly AF, Beckers A. Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients. Eur J Endocrinol. 2012;167:651–62.

Wakil A, Rigby AS, Clark AL, Kallvikbacka-Bennett A, Atkin SL. Low dose cabergoline for hyperprolactinaemia is not associated with clinically significant valvular heart disease. Eur J Endocrinol. 2008;159:R11–4.

Wallaschofski H, Donné M, Eigenthaler M, Hentschel B, Faber R, Stepan H, Koksch M, Lohmann T. PRL as a novel potent cofactor for platelet aggregation. J Clin Endocrinol Metab. 2001;86:5912–9.

Walsh JP, Pullan PT. Hyperprolactinaemia in males: a heterogeneous disorder. Aust NZ J Med. 1997;27:385–90.

Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhoea. Cabergoline Comparative Study Group. N Engl J Med. 1994;331:904–9.

Winters SJ, Troen P. Altered pulsatile secretion of luteinizing hormone in hypogonadal men with hyperprolactinaemia. Clin Endocrinol. 1984;21:257–63.

Wong A, Eloy JA, Couldwell WT, Liu J. Update on prolactinomas. Part 2: treatment and management strategies. J Clin Neurosci. 2015;22:1568–74.

Yavuz D, Deyneli O, Akpinar I, Yildiz E, Gözü H, Sezgin O, Haklar G, Akalin S. Endothelial function, insulin sensitivity and inflammatory markers in hyperprolactinemic pre-menopausal women. Eur J Endocrinol. 2003;149:187–93.

Yazigi RA, Quintero CH, Salameh WA. Prolactin disorders. Fertil Steril. 1997;67:215–25.

Yener S, Comlekci A, Arda N, Men S, Yesil S. Misdiagnosis due to the hook effect in prolactin assay. Med Princ Pract. 2008;17:429–31.

Yu-Lee LY. Prolactin modulation of immune and inflammatory responses. Recent Prog Horm Res. 2002;57:435–55.

Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med. 2007;356:39–46.

Zellweger R, Zhu XH, Wichmann MW, Ayala A, DeMaso CM, Chaudry IH. Prolactin administration following hemorrhagic shock improves macrophage cytokine release capacity and decreases mortality from subsequent sepsis. J Immunol. 1996;157:5748–54.

Zis AP, Haskett RF, Albala AA, Carroll BJ. Morphine inhibits cortisol and stimulates prolactin secretion in man. Psychoneuroendocrinology. 1984;9:423–7.