Chapter 5
Prolactin Excess and Deficiency: Epidemiology, Causes (Excluding Prolactin-Secreting Pituitary Tumors)

Rocío Villar Taibo, Mildred Sifontes Dubon, Ignacio Bernabeu Morón, and Felipe F. Casanueva

Introduction

Prolactin is secreted mostly by the lactotroph cells of the pituitary gland, but other organs and tissues also produce prolactin which may act in a paracrine manner, including the hypothalamus, telencephalon, brain stem, spinal cord, choroid plexus, mammary gland, some immune cells, and circumventricular organs [1]. Nevertheless, ectopic production of prolactin in excess is extremely rare, and prolactin excess or deficiency results almost exclusively from diseases that cause hyper- or hyposecretion of prolactin by lactotroph cells [2].

Prolactin excess accounts for the majority of cases of prolactin alterations and is defined as an increase of serum prolactin above the laboratory reference limit, assuming that the serum sample was obtained without excessive venipuncture stress [3].

Prolactin deficiency can be defined as a loss of function of anterior pituitary cells secreting prolactin, with resulting decreased or absent serum levels of prolactin. It can occur either in association with other anterior pituitary hormone defects or in isolation.

R. Villar Taibo · M. Sifontes Dubon · I. B. Morón
Department of Medicine – Endocrinology, University Hospital of Santiago, Santiago de Compostela, Spain

F. F. Casanueva (✉)
Department of Medicine – Endocrinology, University Hospital of Santiago, Santiago de Compostela, Spain

University of Santiago, and Centro de Investigación Biomédica en Red Obesity-Nutrition, Santiago de Compostela, Spain

Department of Medicine, Santiago de Compostela University, Complejo Hospitalario Universitario de Santiago (CHUS), CIBER de Fisiopatologia Obesidad y Nutrición (CIBERobn), Instituto Salud Carlos III, Santiago de Compostela, Spain
e-mail: endocrine@usc.es

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Normal Levels of Prolactin

Several factors affect prolactin levels:

1. Gender: normal serum prolactin concentration varies with gender. Hence, normal prolactin levels for men and women are different (higher in women).
2. Circadian rhythm: serum prolactin also displays pronounced circadian variation with maximal concentrations occurring during sleep, with a peak of up to 30 ng/ml between 4 and 6 am, reaching a nadir during waking hours.
3. Seasonal changes: prolactin levels are also subject to seasonal changes, being higher in the spring and summer.
4. Menstrual cycle: prolactin levels can change during the menstrual cycle, being higher during the mid and second half of the cycle, compared with follicular phase. It also varies significantly between pre- and postmenopausal women. Therefore, specific reference intervals for each phase of the menstrual cycle are needed, and prolactin levels should be measured in the follicular phase, before the mid-cycle.

On the contrary, food does not appear to affect serum prolactin concentrations; and fasting is not necessary when having serum prolactin measured [4].

Prolactin Excess: Epidemiology and Causes

Hyperprolactinemia represents a common problem in endocrine practice. The prevalence and incidence of hyperprolactinemia depend on the study population. In healthy adults, hyperprolactinemia prevalence seems to vary from 1.2% to 4.1%, but in certain clinical settings, it can increase to 3.9–30%, such in female patients with menstrual abnormalities or infertility [5].

In a recent Scottish epidemiological study, all hyperprolactinemia cases between 1988 and 2014 were reviewed. Over this period the prevalence of hyperprolactinemia increased from 22 to 232 per 100,000. The adjusted incidence of all causes for hyperprolactinemia was 13.8 per 100,000, increasing from 9 to 20 per 100,000 over 20 years. This increasing incidence and prevalence over the study period was attributed mostly to an increase in drug-induced cases, but also an increased recognition of macroprolactin and a rise in pituitary diagnosis for men were observed.

Regarding gender distribution, hyperprolactinemia may occur in both males and females, but a female predominance is usually reported. So, in the PROLEARS study, the incidence in women was 3.5 times that was observed in men, but the gender difference was little above the age of 55 years. The highest incidence rate of hyperprolactinemia was found in women aged 25–34 years (49.6 per 100,000 person-years) [5].

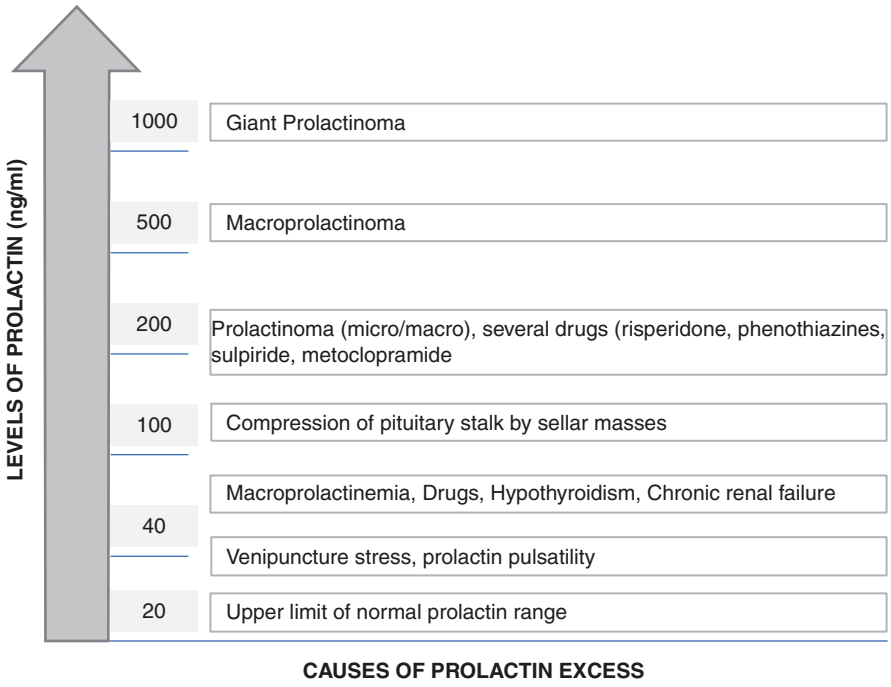

Fig. 5.1 Levels of prolactin and etiologies of hyperprolactinemia

Hyperprolactinemia can be physiological, pathological, or pharmacological [6], but sometimes the cause is unknown (idiopathic hyperprolactinemia). The degree of hyperprolactinemia can help narrow the list of diagnostic possibilities (Fig. 5.1).

Epidemiological data from large clinical series of hyperprolactinemia showed that prolactinomas and other pituitary tumor types are the main cause of hyperprolactinemia (35–70%), followed by idiopathic cases (28–46%). However, the majority of the studies excluded secondary causes of hyperprolactinemia, such us drug-induced hyperprolactinemia. When pharmacological causes are taken into account, they can represent one of the most prevalent etiologies of this condition [7].

Studies addressing pituitary secretion dysfunction following brain injuries have found variable prevalence of hyperprolactinemia in this population. In the first days post-injury, 52–77% of patients may exhibit hyperprolactinemia, but a few months thereafter the prevalence decreases to 3–5.7% [8].

Table 5.1 shows the main causes of hyperprolactinemia registered in epidemiological series [5, 7, 9–14].

Table 5.1 Reported causes of hyperprolactinemia in epidemiological series

Seshadri et al. [9]	Pituitary tumors (35.2%)
n = 71 female patients	Functional hyperprolactinemia (46.4%)
	Drug-induced hyperprolactinemia (7%)
	Hypothyroidism (5.6%)
Sonino et al. [10]	Pituitary adenomas (63.5%)
n = 52 patients (secondary causes of hyperprolactinemia excluded)	Idiopathic hyperprolactinemia (36.5%)
Berinder et al. [11]	Pituitary adenomas (71%)
n = 271 female patients (secondary causes of hyperprolactinemia excluded)	Idiopathic hyperprolactinemia (29%)
Zargar et al. [12]	Pituitary microprolactinoma (35.8%)
n = 187 female patients	Nonfunctioning pituitary adenoma with stalk compression (16%)
	PCOS (12.8%)
	Idiopathic hyperprolactinemia (27.8%)
Vilar et al. [7]	Prolactinomas (56.2%)
n = 1234 patients	Drug-induced hyperprolactinemia (14.5%)
	Macroprolactinemia (9.3%)
	Nonfunctioning pituitary adenomas (6.6%)
	Primary hypothyroidism (6.3%)
	Idiopathic hyperprolactinemia (3.6%)
	Acromegaly (3.2%)
Saejong et al. [13]	Pituitary adenoma 40.2%
n = 139 female patients	Idiopathic hyperprolactinemia 37.1%
Dekkers et al. [14]	Females: pituitary adenoma (70%), idiopathic or drug-associated hyperprolactinemia (30%)
n = 229 patients	
	Males: pituitary macroadenoma (62%)
Soto-Pedre et al. [5]	Drug-induced hyperprolactinemia (45.9%)
n = 1301	Pituitary disorder (25.4%)
	Macroprolactin (7.5%)
	Hypothyroidism (6.1%)
	Idiopathic (15%)

Physiologic Causes

Serum prolactin concentrations normally increase substantially during several physiological situations.

Pregnancy

Throughout pregnancy, the increasing estradiol concentration leads to a prolactin increase, reaching its peak at delivery. The magnitude of the increase is quite variable (ranging from 35 to 600 ng/mL). Estradiol secretion decreases after delivery. Several weeks postpartum, the basal serum prolactin concentration usually normalizes, even when the mother is breastfeeding [15].

Nipple Stimulation and Lactation

Nipple stimulation during breastfeeding transiently increases serum prolactin concentrations, presumably via a neural pathway. This increase is directly proportional to the degree of preexisting lactotroph hyperplasia due to estrogen. In the first weeks postpartum, as an example, the serum prolactin concentration increases up to 300 ng/mL above baseline in response to suckling; in contrast, several months after delivery, the increase in prolactin in response to suckling in the breastfeeding woman is usually less than 10 ng/mL above baseline [15].

In nonlactating women and men, nipple stimulation, breast imaging (mammography, ultrasound), or breast examination may but does not usually increase prolactin secretion.

Stress

Physical or psychological stress can cause hyperprolactinemia. As with all stimuli of prolactin secretion, women have greater increases than men, presumably due to the effect of their higher serum estradiol concentrations on the lactotroph cells. The magnitude of the increase in prolactin in response to stress is small, so the values rarely exceed 40 ng/mL.

Other

Sexual intercourse and acute exercise are also physiological, well-described causes of transient prolactin elevation.

Pathologic Causes

If we exclude lactotroph adenomas, we can identify several causes of pathological prolactin elevations (Fig. 5.2).

Decreased Dopaminergic Inhibition of Prolactin Secretion

Several conditions interfere with normal dopamine inhibition of prolactin secretion. These include any damage to the dopaminergic neurons of the hypothalamus, pituitary stalk section, or any disease in or near the hypothalamus-pituitary area that interferes with the secretion or delivery of dopamine to lactotrophs:

1. Tumors: adenomas of the pituitary other than lactotroph adenomas, craniopharyngiomas, germinomas, meningiomas, or malignant lesions (e.g., metastatic breast carcinoma).
2. Infiltrative diseases of the hypothalamus (e.g., tuberculosis, histiocytosis X, sarcoidosis).

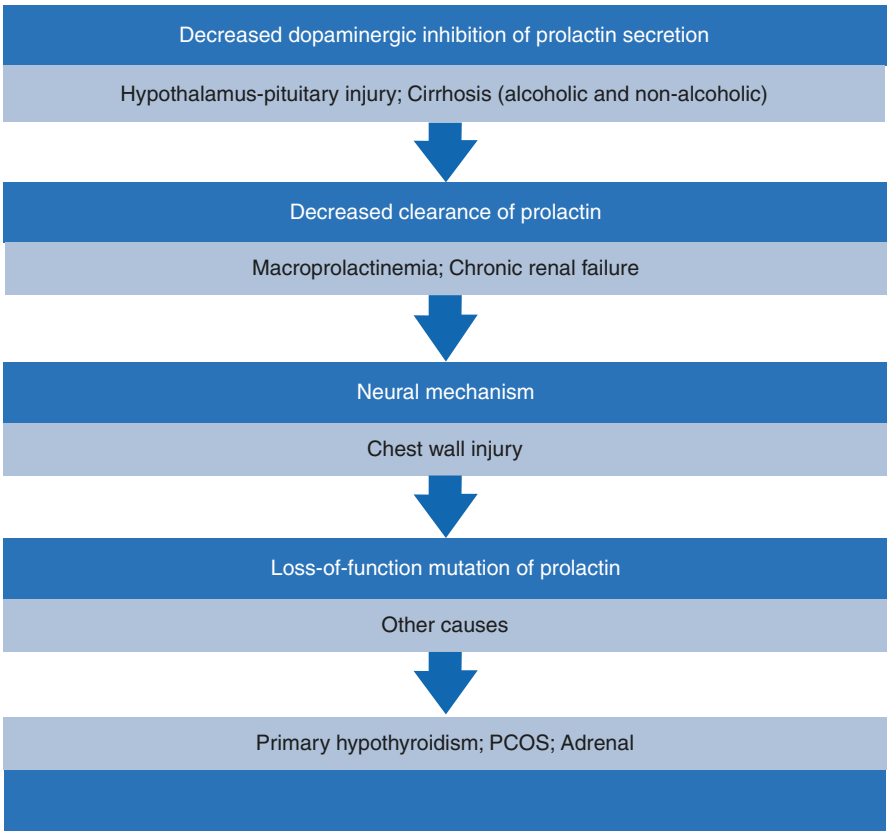

Fig. 5.2 Mechanisms of pathological hyperprolactinemia

3. Section of the hypothalamus-pituitary stalk (e.g., due to head trauma or surgery).
4. Irradiation to hypothalamus-pituitary region.

Alcoholic and nonalcoholic cirrhosis may be associated with elevated basal prolactin levels in 5–20% of these patients, possibly owing to alterations in hypothalamic dopamine generation [16].

Decreased Clearance of Prolactin

Chronic renal failure and macroprolactinemia are two causes of hyperprolactinemia due to decreased clearance of prolactin.

1. Chronic renal failure: the serum prolactin concentration is high in patients who have chronic renal failure and returns to normal after renal transplantation. Although there is a one-third decrease in metabolic clearance rate, a threefold increase in prolactin secretion can also be observed.

2. Macroprolactinemia: macroprolactin results from the formation of prolactin-immunoglobulin complexes that range in size from approximately 150 to 170 kD. These complexes are immunologically detectable, and macroprolactinemia is associated with apparent hyperprolactinemia although not typically associated with clinical features, due to its limited bioavailability and bioactivity. Although this entity is not of clinical significance directly, it is of clinical significance indirectly because it can be misdiagnosed and treated as prolactin hypersecretion. Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin.

Prolactin Increase Due to Neural Mechanism

Chest wall injuries, such as severe burns, herpes zoster, trauma, or surgery, can increase prolactin secretion, presumably through stimulation of afferent neural pathways.

Genetic Causes: Germline Loss-of-Function Mutation

High levels of prolactin and prolactin insensitivity can be found in some families with a germline, loss-of-function mutation in the prolactin receptor gene (*PRLR*). The heterozygous mutation in *PRLR* results in an amino acid change from histidine to arginine at codon 188, leading to a loss of downstream signaling by Janus kinase 2 (JAK2) and signal transducer and activator of transcription factor 5 (STAT5). The presence of oligomenorrhea and infertility in these cases suggests that the hyperprolactinemia is having a biologic effect, which in turn suggests that there are functioning prolactin receptors in some tissues [17].

Other Causes

3. Primary hypothyroidism: although prolactin concentrations are normal in most hypothyroid patients, primary hypothyroidism can be a cause of hyperprolactinemia. The mechanism of hyperprolactinemia in hypothyroidism is not known. Both enhanced hypothalamic synthesis of thyrotropin-releasing hormone (TRH) and increased pituitary responsiveness to TRH have been described, and the serum prolactin response to stimuli, such as TRH, is increased. Prolactin values return to normal when hypothyroidism is corrected. It is important to note that severe primary hypothyroidism is a potential cause of an enlarged pituitary gland (due to thyrotroph hyperplasia, lactotroph hyperplasia, or both) and not to confuse this entity with a lactotroph adenoma.
4. Polycystic ovary syndrome (PCOS): PCOS and hyperprolactinemia are usually associated in clinical practice. However, there is no proof of a

pathophysiological link between these two entities [18]. Analysis of the evidence linking PCOS and hyperprolactinemia suggests that these conditions have independent origins and the association seems to be fortuitous. Recent investigations using serial serum sampling have excluded transient elevations of prolactin and have shown a less frequent association between these disorders [19]. PCOS patients with increased prolactin levels must be investigated for other causes of hyperprolactinemia, and in the majority of them, another cause can be found (pituitary adenoma in 69%, pharmacological hyperprolactinemia in 23%, and macroprolactin in 8%) [20].

5. Adrenal insufficiency: hyperprolactinemia has been described in patients with adrenal insufficiency, and cortisol replacement corrects it. This suggests that glucocorticoids modulate prolactin secretion, with a suppressive effect on prolactin gene transcription and prolactin release [21].

Pharmacological Causes

Drugs are a frequent cause of hyperprolactinemia, although they do not cause lactotroph adenomas. In a Brazilian multicenter study of hyperprolactinemia, drug-induced hyperprolactinemia was the second main cause, after prolactinomas, with a prevalence of 14.5% [7]. However, in the recent PROLEARS study, drugs became the leading cause of hyperprolactinemia (45.9%) and tripled during the 20 years of follow-up of the study. Antipsychotic and antidepressant medications were the most frequent etiology, representing 63.5% and 12.7% of the cases of drug-induced hyperprolactinemia, respectively. The increased rate of drug-induced hyperprolactinemia probably reflects a higher use of psychotropic medications over the study period [5].

In medication-induced hyperprolactinemia, serum prolactin concentrations are typically in the 25–100 ng/mL range. One exception is the antipsychotic drug, risperidone, which may be associated with serum prolactin concentrations as high as 200 ng/mL.

Antipsychotics

Antipsychotics are the most common cause of pharmacologically induced hyperprolactinemia, and the association between antipsychotic medication and hyperprolactinemia has been under investigation since at least the 1970s. Some of the antipsychotic drugs are known dopamine D_2 receptor antagonists and raise serum prolactin by that mechanism. Serum prolactin concentrations increase within hours after acute administration of the drug and return to normal within 2–4 days after cessation of chronic therapy.

Although hyperprolactinemia can be found with all antipsychotic medications, the magnitude of the elevation varies among drugs. First-generation antipsychotics,

like haloperidol or sulpiride, induce a significant rise in serum prolactin, two or three times above the reference values. It has been suggested that patients receiving long-term neuroleptic treatment may develop tolerance, with normalization of prolactin with continued treatment. However, this is not clear and other studies reported that tolerance does not occur.

Several second-generation antipsychotics cause a lesser elevation of the prolactin plasma levels than first-generation ones. Their greater specificity, resulting in a lesser blockade of the dopaminergic receptor but also their stronger blockade of serotonin receptors, may explain the limited elevation of prolactin. As exceptions, amisulpride, risperidone, and paliperidone are associated with higher levels of hyperprolactinemia. On the contrary, clozapine, quetiapine, olanzapine, ziprasidone, and aripiprazole are considered "prolactin-sparing antipsychotics," but prolactin excess can occur in association with their use, too [4].

Prolactin increase with antipsychotic medication has no clinical relevance in most patients, and generally no treatment is needed (unless hypogonadism or bothersome galactorrhea result). It is usually greater in females than in males, probably due to priming by estrogen. Also, prolactin levels are significantly lower in current and ex-cigarette smokers on antipsychotic medications, compared with nonsmokers. Smoking may reduce serum concentration of some antipsychotic drugs due to induction of the hepatic cytochrome P450 1A2 enzyme, and this can lead to a reduction in prolactin levels [22].

Antidepressants

Tricyclic agents and monoamine oxidase inhibitors are a common cause of hyperprolactinemia.

Selective serotonin reuptake inhibitors can cause little, if any, increase in the serum prolactin concentration, and they do not appear to cause clinically significant hyperprolactinemia in most patients.

Gastric Motility Drugs

Metoclopramide and domperidone are dopamine D2 receptor antagonists and can raise serum prolactin.

Antihypertensive Drugs

Methyldopa, which is a not commonly used antihypertensive drug, increases prolactin secretion by an inhibition of dopamine synthesis.

Verapamil is the only calcium channel blocker associated with a rise in prolactin levels, but the mechanism is not known. It can affect 8.5% of drug users and in most cases prolactin levels return to normal after drug cessation [23].

Estrogens

Estrogens have the ability to elevate prolactin and enhance responsiveness to prolactin-releasing stimuli. The mechanism by which estrogen stimulates prolactin secretion appears to involve binding of estrogen to the estrogen receptor, which then binds to an estrogen response element on the prolactin gene in the lactotroph cell. Estrogens increase the number of lactotroph cells of the anterior pituitary and act on the hypothalamus to decrease dopamine content [24].

Nevertheless, the amount of estrogen in hormonal contraceptives generally does not cause significant hyperprolactinemia.

Opioids

Opioids, like morphine or methadone, may both inhibit gonadal function and cause hyperprolactinemia [25].

Other Drugs

1. Cocaine use seems to influence prolactin levels (higher values in cocaine- dependent patients than controls) [26].
2. Cimetidine, an H2 antagonist, produces robust, transient increase in plasma prolactin levels in man following intravenous administration. This effect has been attributed, in part, to indirect central serotonergic mechanisms involving 5-HT2 receptors in the hypothalamus, but the evidence is inconclusive [27].

Idiopathic Hyperprolactinemia

In a substantial number of patients with hyperprolactinemia, no cause can be found, and they are classified as idiopathic. In these cases, serum prolactin concentration usually ranges between 20 and 100 ng/mL. Although many of these patients may have microadenomas not visible on imaging studies, in most of them, the serum prolactin concentrations change little during follow-up for several years.

Idiopathic hyperprolactinemia was one of the most reported etiologies in the past (28–46% of causes) [10–14], but in the recent study PROLEARS, it represented only 15%, maybe due to a better recognition of pathological causes [5].

Prolactin Deficiency: Epidemiology and Causes

Prolactin has a role in breast growth, lactogenesis during pregnancy, and the initiation and maintenance of lactation after delivery. Hypoprolactinemia has been reported to adversely affect fertility. In women, the luteal phase of the menstrual

cycle can be altered in the context of prolactin deficiency [28]. Some authors have concluded that a minimal amount of prolactin is necessary for normal ovulatory function. However, the role of prolactin in human ovulation is not clear, and there are reports of women who, despite undetectable prolactin levels, conceived without any medical assistance. In men, low PRL has been associated with reduced ejaculate and seminal vesicle volume in infertile subjects. In addition, among men consulting for sexual dysfunction, hypoprolactinemia has been associated with erectile dysfunction and premature ejaculation, findings further confirmed in the general European population and infertile men [29].

Hypoprolactinemia may appear in the context of several pathological conditions or pharmacological treatments. Isolated prolactin deficiency is rare; most patients with acquired prolactin deficiency have evidence of other pituitary hormone deficiencies [30]. In fact, the incidence of acquired hypoprolactinemia increases with the number of other anterior pituitary defects and should be considered a marker of extensive pituitary damage.

According to a Spanish epidemiological study, the prevalence of hypopituitarism was 29 of 100,000 in 1992, and it increased to 45.5 of 100,000 in 1999, with an average annual incidence of 4.2 cases of 100,000 (similar for men and women). The most frequent causes included pituitary tumor (61%), non-pituitary tumor (9%), and a nontumor cause (30%). With regard to the type of hormonal deficiencies, LH/FSH defect was the most prevalent, and it was present in 87% of the cases, while prolactin deficiency was the least frequent (17%) [31]. However, epidemiological data of prolactin deficiency are scarce in literature. Most studies of hypopituitarism do not report prolactin deficiency, and this may be the result of a perceived lack of significance relative to other pituitary hormones.

Pathological Causes

Any disease involving the hypothalamus-pituitary area can affect the secretion of one or more of pituitary hormones, including prolactin. The most recognized causes of hypopituitarism are summarized in Table 5.2 [32].

One of the most relevant and identified etiologies of hypoprolactinemia is Sheehan's syndrome, due to its presentation with alactogenesis.

Sheehan's Syndrome

Sheehan's syndrome is a postpartum pituitary necrosis, usually precipitated by massive uterine hemorrhage during the peripartum or postpartum period. It is a leading cause of hypopituitarism in underdeveloped or developing countries but is rare in developed countries, due to improvements in obstetrical care. A recent Turkish study showed that this syndrome was present in 13.8% of patients with hypopituitarism, compared with 3.1% in developed countries.

Table 5.2 Causes of hypopituitarism

Neoplastic	Pituitary and non-pituitary tumors
	Metastases
	Hematological malignancy
Iatrogenic	Surgery in the hypothalamus-pituitary area
	Cranial irradiation
Head trauma	Traumatic brain damage
Infiltrative/inflammatory	Sarcoidosis
	Langerhans cell histiocytosis
	Amyloidosis
	Hemochromatosis
	Lymphocytic hypophysitis
	Wegener's granulomatosis
Infectious	Tuberculosis
	Meningitis
	Syphilis
	Bacterial, viral, parasitic, or fungal infections
	Pituitary abscess
Vascular	Sheehan's syndrome
	Pituitary apoplexy
	Ischemic stroke
	Aneurysm
	Subarachnoid hemorrhage
	Snake bites (Russell's viper bites)
Congenital	Isolated or multiple pituitary hormone deficiencies
Other	Primary empty sella
	Congenital chronic hydrocephalus

The onset of hypopituitarism is usually insidious, with nonspecific symptoms, and there is often a delay in diagnosis of several years or even decades. A history of postpartum hemorrhage so severe as to cause hypotension and require blood transfusion may be crucial to establish the etiology of hypopituitarism.

In severe cases, the presentation can be acute, with lethargy and anorexia. In mild cases, the inability to breastfeed due to prolactin deficiency is a frequent symptom, along with the absence of menses after delivery, loss of sexual hair, fatigue, anorexia, or weight loss. An evaluation of pituitary function should be done after a delivery associated with heavy blood loss, especially the adrenal axis, and initiate replacement treatment as needed. The value of measuring prolactin shortly after postpartum hemorrhage to predict the ability to breastfeed has not been studied. Hypopituitarism is progressive, with no recovery of the pituitary function. In the chronic phase, the MRI may reveal a complete or partial empty sella [32].

Genetic Causes

There are some genetic mutations that cause prolactin deficiency, most of them in combination with other hormone defects.

1. Multiple anterior pituitary hormone deficits (MPHD): familial occurrence of MPHD is unusual and has been described as being transmitted in an autosomal recessive, autosomal dominant, or X-linked recessive manner.

HESX1, LHX3, and LHX4 transcription factors are important for pituitary organogenesis and early differentiation of several types of pituitary cells. Mutations in the genes encoding these factors cause combined pituitary hormone deficiency (GH, prolactin, TSH, LH, and FSH) [33].

PROP-1 is necessary for the differentiation of a cell type that is a precursor to somatotroph, lactotroph, thyrotroph, and gonadotroph cells. Mutations in *PROP-1* appear to be the most common cause of both familial and sporadic congenital combined pituitary hormone deficiency (gonadotropin deficiency in addition to GH, TSH, and prolactin deficiency) [34–35].

PIT-1 (called POU1F1 in the human) acts temporally just after PROP-1 and is necessary for the differentiation of a cell type that is a precursor of somatotroph, lactotroph, and, to a lesser degree, thyrotroph cells. Both dominant and recessive mutations of the gene that encodes PIT-1 lead to congenital deficiencies of GH, prolactin, and sometimes TSH. The secretion of ACTH, FSH, and LH is preserved. Circulating anti-PIT-1 antibodies may also result in hypopituitarism.

Combined prolactin deficiency has also been reported in genetic defects of G proteins underlying the resistance to PTH (pseudohypoparathyroidism), although an associated autoimmune process is hypothesized as being responsible for the prolactin deficiency [36].

2. Isolated prolactin deficiency: an isolated prolactin deficiency without a pharmacological, pathological, or iatrogenic cause is a rare entity of which only a few cases have been reported, usually presenting as puerperal alactogenesis [37, 38]. In these patients, breast milk production does not respond to stimulation with antidopaminergic drugs (domperidone) but is restored with recombinant human prolactin. The lack of response to antidopaminergic drugs, as well as the restoration of milk production upon recombinant human prolactin administration, indicate the existence of a specific defect in lactotroph cells, due to genetic or autoimmune causes. A genetic basis is possible, because in one of these cases a familial occurrence of alactogenesis was reported [38]. Maybe minor or partial mutations of the *PIT1* or *PROP1* genes may be associated with the occurrence of prolactin deficiency. However, in another case, a mutation in the coding region of prolactin gene and its putative releasing hormone or receptor or in other genes related to MPHD could not be demonstrated. Instead, the authors demonstrated the presence of circulating autoantibodies recognizing some antigens in prolactin-secreting cells but not the hormone itself or any other pituitary cells or hormones, suggesting an autoimmune etiology [39].

Pharmacological

Dopamine Agonists

Dopamine agonists are used in high doses in patients with Parkinson's disease. They can cause isolated prolactin suppression in a significant percentage of individuals (44%), especially those with a high rate of exposure to newer dopamine agonists [40].

Aripiprazole

Aripiprazole is a non-prolactin-raising antipsychotic which has been proposed as an alternate option to treat risperidone-associated hyperprolactinemia. However, doses higher than 5 mg can reduce prolactin levels to lower than 3 ng/mL, causing prolactin deficiency [41].

Conclusion

Prolactin disorders are common in clinical practice, especially hyperprolactinemia. An increasing incidence and prevalence is being reported, and it has been attributed mostly to a rise in drug-induced cases but also increased recognition of other causes of prolactin alteration, including genetic causes.

References

1. Bernichtein S, Touraine P, Goffin V. New concepts in prolactin biology. J Endocrinol. 2010;206(1):1–11.
2. Molitch ME, Schwartz S, Mukherji B. Is prolactin secreted ectopically? Am J Med. 1981;70(4):803–7.
3. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88.
4. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs. 2014;28:421–53.
5. Soto-Pedre E, Newey PJ, Bevant JS, Greig N, Leese GP. The epidemiology of hyperprolactinaemia over 20 years in the Tayside region of Scotland: the Prolactin Epidemiology, Audit and Research Study (PROLEARS). Clin Endocrinol (Oxf). 2017;86:60–7.
6. Mancini T, Casanueva FF, Giustina A. Hyperprolactinemia and prolactinomas. Endocrinol Metab Clin N Am. 2008;37(1):67–99.
7. Vilar L, Freitas MC, Naves LA, et al. Diagnosis and management of hyperprolactinemia: results of a Brazilian multicenter study with 1234 patients. J Endocrinol Investig. 2008;31:436–44.
8. Scranton RA, Baskin DS. Impaired pituitary axes following traumatic brain injury. J Clin Med. 2015;4:1463–79.
9. Seshadri MS, Sud A, Chandy MJ, Thomas J, Kanagasbapahy AS, Cherian AM. Hyperprolactinemia in women- a series of 71 cases. J Assoc Physicians India. 1993;41:706–7.

10. Sonino N, Navarrini C, Ruini C, Fallo F, Boscaro M, Fava GA. Life events in the pathogenesis of hyperprolactinemia. Eur J Endocrinol. 2004;151:61–5.
11. Berinder K, Stackenäs I, Akre O, Hirschberg AL, Hulting AL. Hyperprolactinemia in 271 women: up to three decades of clinical follow-up. Clin Endocrinol (Oxf). 2005;63(4):450–5.
12. Zargar AH, Laway BA, Massodi SR, et al. Clinical and etiological profile of hyperprolactinemia-data from a tertiary care centre. J Assoc Physicians India. 2005;53: 288–90.
13. Saejong R, Dangrat C, Techatrisak K, Angsuwatthana S, Rattanachaivanont M, Tanmahasamut P. Hyperprolactinemia: a 12-year retrospective study at gynecologic endocrinology unit, Siriraj hospital. J Med Assoc Thail. 2013;96:1247–56.
14. Dekkers OM, Ehrenstein V, Bengtsen M, et al. Breast cancer risk in hyperprolactinemia: a population-based cohort study and meta-analysis of the literature. Eur J Endocrinol. 2015;173:269–73.
15. Tyson JE, Hwang P, Guyda H, Friesen HG. Studies of prolactin secretion in human pregnancy. Am J Obstet Gynecol. 1972;113(1):14–20.
16. Molitch ME. Disorders of prolactin secretion. Endocrinol Metab Clin N Am. 2001;30(3):585–610.
17. Newey PJ, Gorvin CM, Cleland SJ, et al. Mutant prolactin receptor and familial hyperprolactinemia. N Engl J Med. 2013;369:2012–20.
18. Robin G, Catteau-Jonard S, Young J, Dewailly D. Physiopathological link between polycystic ovary syndrome and hyperprolactinemia: myth or reality? Gynecol Obstet Fertil. 2011;39(3):141–5.
19. Bracero N, Zacur HA. Polycystic ovary syndrome and hyperprolactinemia. Obstet Gynecol Clin N Am. 2001;28(1):77–84.
20. Filho RB, Domingues L, Naves L, Ferraz E, Alves A, Casulari LA. Polycystic ovary syndrome and hyperprolactinemia are distinct entities. Gynecol Endocrinol. 2007;23(5):267–72.
21. Stryker TD, Molitch ME. Reversible hyperthyrotropinemia, hyperthyroxinemia, and hyperprolactinemia due to adrenal insufficiency. Am J Med. 1985;79(2):271–6.
22. Mackin P, Waton A, Nulkar A, Watkinson HM. Prolactin and smoking status in antipsychotic-treated patients. J Psychopharmacol. 2011;25(5):698–703.
23. Romeo JH, Dombrowski R, Kwak YS, Fuehrer S, Aron DC. Hyperprolactinaemia and verapamil: prevalence and potential association with hypogonadism in men. Clin Endocrinol (Oxf). 1996;45:571–5.
24. Veselinovic T, Schorn H, Vernaleken IB, Schiffl K, Klomp M, Gründer G. Impact of different antidopaminergic mechanisms on the dopaminergic control of prolactin secretion. J Clin Psychopharmacol. 2011;31(2):214–20.
25. Merdin A, Merdin FA, Gündüz S, Bozcuk H, Coskun HS. Opioid endocrinopathy: a clinical problem in patients with cancer pain. Exp Ther Med. 2016;11(5):1819–22.
26. Patkar AA, Mannelli P, Certa KM, et al. Relationship of serum prolactin with severity of drug use and treatment outcome in cocaine dependence. Psychopharmacology (Berl). 2004;176(1):74–81.
27. Meltzer HY, Maes M, Lee MA. The cimetidine-induced increase in prolactin secretion in schizophrenia: effect of clozapine. Psychopharmacology (Berl). 1993;112(1 Suppl):S95–104.
28. Kauppila A, Martikainen H, Puistola U, Reinila M, Romberg L. Hypoprolactinemia and ovarian function. Fertil Steril. 1988;49:437–41.
29. Rastrelli G, Corona G, Maggi M. The role of prolactin in andrology: what is new? Rev Endocr Metab Disord. 2015;16(3):233–48.
30. Mukherjee A, Murray RD, Columb B, Gleeson HK, Shalet SM. Acquired prolactin deficiency indicates severe hypopituitarism in patients with disease of the hypothalamic-pituitary axis. Clin Endocrinol (Oxf). 2003;59:743–8.
31. Regal M, Páramo C, Sierra SM, García-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. Clin Endocrinol (Oxf). 2001;55(6):735–40.

32. Pekic S, Popovic V. Diagnosis of endocrine disease: expanding the cause of hypopituitarism. Eur J Endocrinol. 2017;176(6):R269–82.
33. Romero CJ, Pine-Twaddell E, Radovick S. Novel mutations associated with combined pituitary hormone deficiency. J Mol Endocrinol. 2011;46(3):R93–102.
34. Rosebloom AL, Almonte AS, Brown MR, Fisher DA, Baumbach L, Parks JS. Clinical and biochemical phenotype of familial anterior hypopituitarism from mutation of the PROP1 gene. J Clin Endocrinol Metab. 1999;84:50–7.
35. Cogan JD, Wu W, Phillips JA 3rd, Arnhold IJ, Agapito A, Fofanova OV, et al. The PROP1 2-base pair deletion is a common cause of combined pituitary hormone deficiency. J Clin Endocrinol Metab. 1998;83:3346–9.
36. Carlson HE, Brickman AS, Bottazo GF. Prolactin deficiency in pseudohypoparathyroidism. N Engl J Med. 1977;296(3):140–4.
37. Douchi T, Nakae M, Yamamoto S, Iwamoto I, Oki T, Nagata Y. A woman with isolated prolactin deficiency. Acta Obstet Gynecol Scand. 2001;80(4):368–70.
38. Zargar AH, Masoodi SR, Laway BA, Shah NA, Salahudin M. Familial puerperal alactogenesis: possibility of a genetically transmitted isolated prolactin deficiency. Br J Obstet Gynaecol. 1997;104(5):629–31.
39. Iwama S, Welt CK, Romero CJ, Radovick S, Caturegli P. Isolated prolactin deficiency associated with serum autoantibodies against prolactin-secreting cells. J Clin Endocrinol Metab. 2013;98(10):3920–5.
40. Daniel JS, Govindan JP, Kamath C, D'Souza C, Adlan MA, Premawardhana LD. Newer dopaminergic agents cause minimal endocrine effects in idiopathic Parkinson's disease. Clin Med Insights Endocrinol Diabetes. 2014;7:13–7.
41. Lozano R, Marín R, Santacruz MJ. Prolactin deficiency by aripiprazole. J Clin Psychopharmacol. 2014;34:539–40.