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Physiological and Pathological Hyperprolactinemia: Can We Minimize Errors in the Clinical Practice?

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Additional information is available at the end of the chapter

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1. Introduction

Human prolactin is a single-chain polypeptide hormone. It has a molecular weight of approximately 22,500 Da (figure 1). It takes part in lactation through physiological and biochemical events.

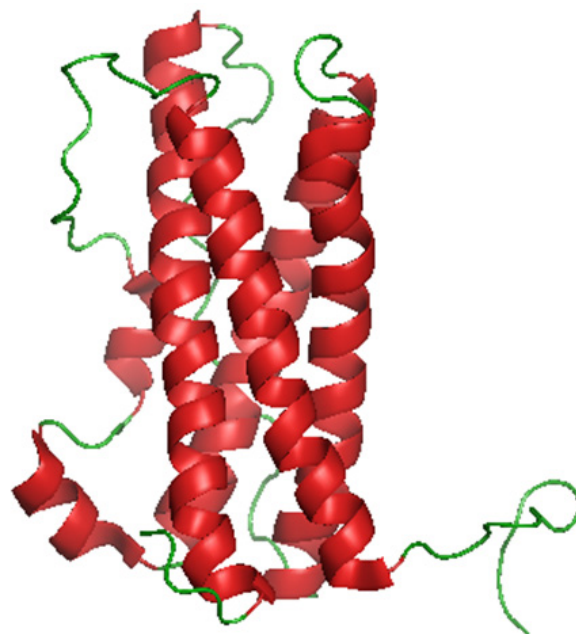
Its polypeptide chain consists of 198-200 amino acid remainders which complete sequence is unknown. Over 80% of the first 50 amino acids are identical or equivalent to the bovine prolactin.

The prolactin molecule is arranged in a single chain of amino acids with three intra molecular disulfide bonded between six cysteine residues (Cys4-Cys11, Cys58-Cys174, Cys191-Cys199 in humans). The sequence homology can vary from the striking 97% among primates to as low as 56% in rodents (1)

The sequence of the first 23 amino acid remainders corresponding to the N-terminal extreme NH₂-leu-pro-ile-cys-pro-gly-ala-ala-arg-cys-gln-val-thr-leu-arg-asp-leu-phe-asp-arg-ala-val

It's secreted by the anterior part of the hypophysis, the adenohypophysis (figure 2) that stimulates the milk production in the mammary glands and the progesterone synthesis in the corpus luteum.

Although the major form of prolactin found in the pituitary gland is 23 kDa, variants of prolactin have been characterized in many mammals, including humans. Prolactin variants can be results of alternative splicing of the primary transcript, proteolytic cleavage and other posttranslational modifications of the amino acid chain (1)

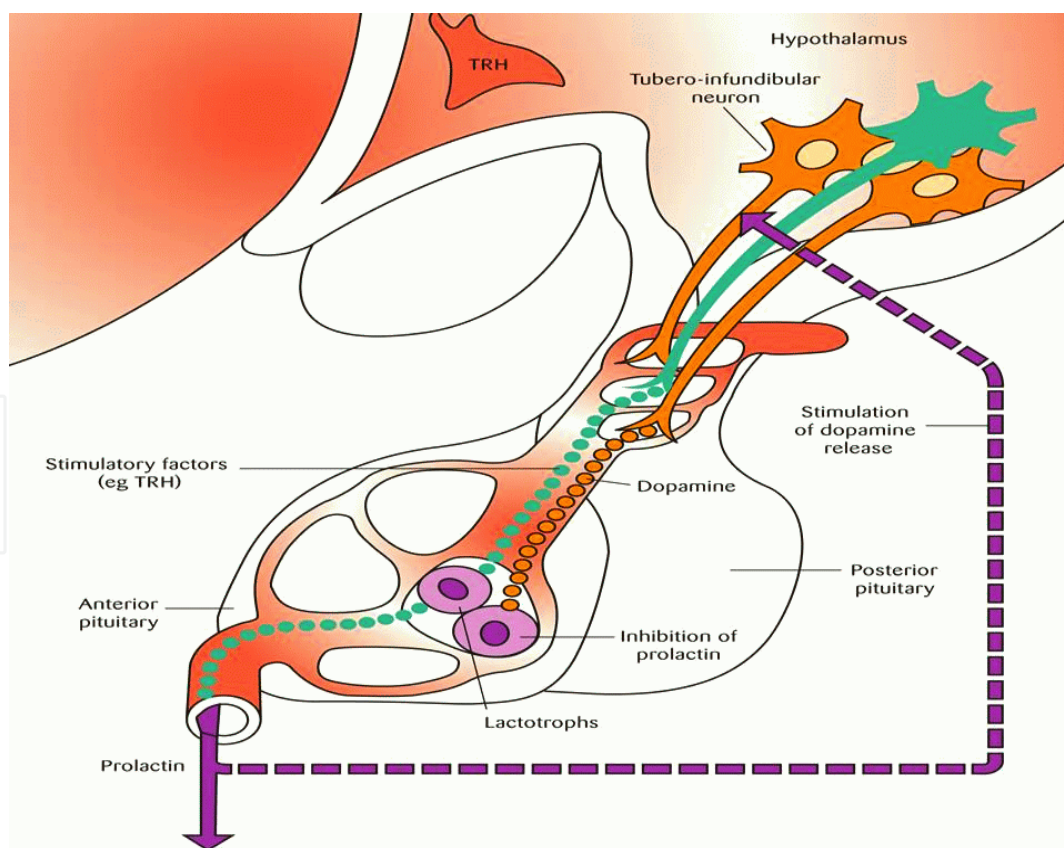


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Figure 1. Prolactin's structure



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Figure 2. Prolactin's secretion.

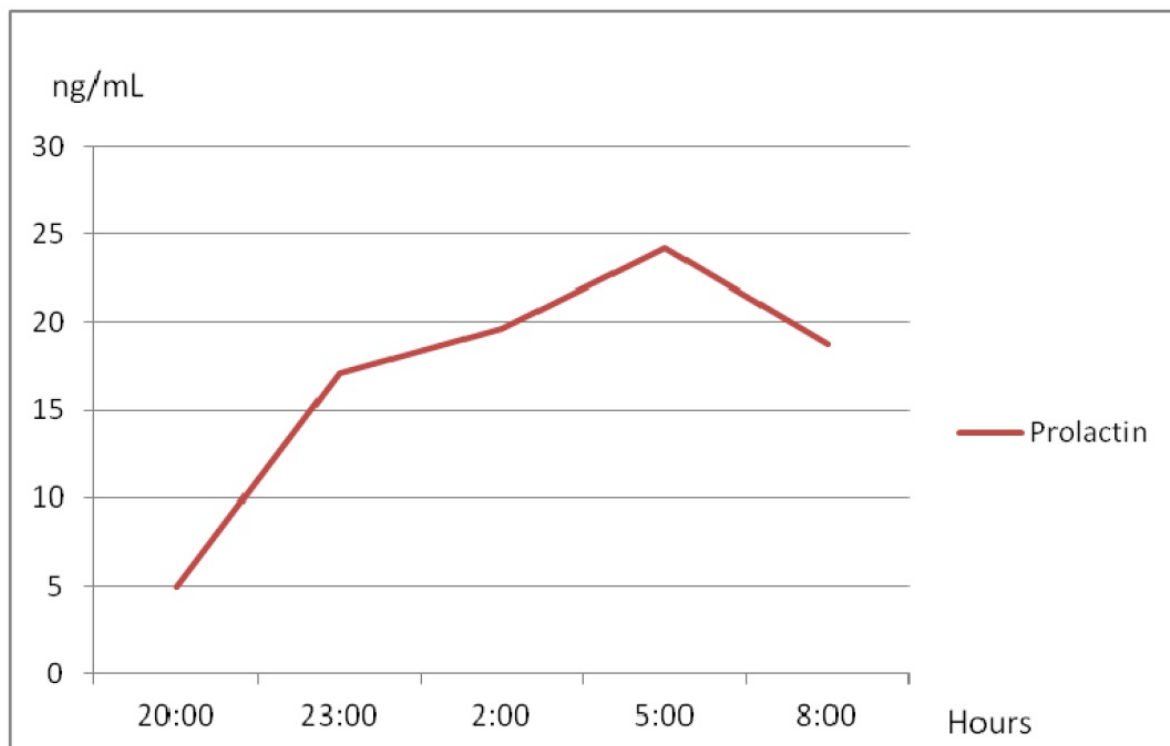
It was discovered in 1928 in a cow's hypophysis and it is phylogenetically considered as the oldest known hormone in the animal kingdom. It has been detected in insects, amphibian, fish and mammals. Its luteotrophic activity was not discovered until 1945 (2-4).

Its isolation was difficult due to its structure, which is similar (in a 16%) to the growth hormone (GH) structure. Both are located in the hypophysis, but the GH is present in higher concentration. Its existence was demonstrated through a trial series performed between 1965 and 1971, it was discovered, as well, the way its secretion is performed, where some physiological factors are positive and negative hypothalamic neurohormonal compounds (5-6).

Studies on the secondary structure of prolactin have shown that 50% of the amino acid chain is arranged in α -helices, while the rest of it forms loops. Although it was predicted earlier, there are still no direct data about the three-dimensional structure of prolactin. The tertiary structure of prolactin was predicted by homology modeling approach, based on the structural similarities between prolactin and other helix bundle proteins, especially growth hormone.

According to the current three-dimensional model, prolactin contains four long α -helices arranged in antiparallel fashion (1).

It shows a synergic effect with the following hormones: estrogens, progesterone and GH.



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Figure 3. Prolactin's circadian rhythm

The nipple suction during breastfeeding favors a bigger amount of hormone synthesis. Besides, it's one of the few physiological systems that have positive feedback, so the presence of prolactin in the organism favors this peptide production.

Nipple and areola's terminal nerves are stimulated when suction occurs. This stimulus travels via afferent nerve pathways to the hypothalamus, proving the prolactin release, by inhibition of the release of dopamine. (5-9)

Prolactin levels during pregnancy rise from its normal value up to 200 or 400 ng/ml. This increase starts around the 8th week in a simultaneous way with the estrogen increasing. The rising in prolactin secretion is due to the suppression that estrogens provoke over dopamine and the direct stimulation of the transcription of the prolactin gene in the hypophysis. (8)

Prolactin shows a circadian and pulsatile rhythm (figure 3) that starts raising 90 minutes after sleep beginning, with maximum peaks at 4-5 hours and it can stay high two hours after waking up (7-9).

It is known that its discharges are 20-30 minutes intervals and the mean life is 20-30 minutes (7-11).

The main circulating form is the monomeric prolactin (little prolactin) or native prolactin which is a non-glycosylated monomer that makes up the 80-90% of the total amount of prolactin in a normal individual.

Another circulating form is the big prolactin (big PRL) which consist in glycosylated dimers or trimers of 40.000-50000 daltons molecular weight, which is supposed to be a deposit form which is rarely detected in serum and which biological activity is nearly non-existent. However, it is detected in hyperprolactinemia without any pathological clinical signs.

Finally, big-big prolactin or macroprolactin which is a dimer form of the big-PRL joined to IgG immunoglobulin with a molecular weight over 100000 daltons and without any biological activity (10-12).

2. Effects

The prolactin's main function in women is to stimulate and maintain the puerperal breastfeeding, direct action over acidophilic cells known as lactotrophs cells of the mammary glands (6, 13). Estrogens, GH, corticoids, placental lactogenic hormones and prolactin are needed to increase the ductal system. Estrogens, progesterone and prolactin are needed to develop the lobuloalveolar system, so levels of these hormones should be considered in pathological states as fibrocystic mastopathy, mastodynia (breast pain), mammary carcinoma, etc.

Among its effects over the mammary alveolar cells there is an increase of the lactose synthesis and a higher production of lactose proteins as casein and lactalbumin.

It is related with the reproductive cycle, the pregnancy maintenance and the fetal growth, through an effect over the mother metabolism acting over different effector organs to facilitate its functions through synergy or inhibition of other hormones.

It shows a synergism with the gonadal steroid hormones in the continuance of the corpus luteum and progesterone production, with action in the reproductive processes, according to some researches that revealed the presence of specific prolactin receptors in the mammal's ovaries, transferring part of the progesterone function which, among other functions, stimulates the formation of membrane receptors for the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) for the follicle growth and the estradiol synthesis. It was found, in the little antral follicles, a prolactin concentration 6 times higher than in circulation, when the follicle is 6-8 mm of diameter the levels drop, getting close to the basal blood levels near the ovulation (3, 4, 12, 14).

Some secondary functions or less powerful have been reported, being related to androgenesis that takes part in the suprarenal cortex reticular area, where some specific receptors for prolactin have been found, the joint with those receptors stimulates the secretion of **dehydroepiandrosterone** and its sulfate.

Prolactin has also an inhibitory effect over the gonadotropin secretion, so its hypersecretion can cause oligomenorrhea or amenorrhea in women (3,4, 14).

In men, the prolactin behavior can affect the adrenal function, the electrolytic balance, gynecomastia, galactorrhea sometimes, libido decreasing and sexual impotence and some other actions in prostate, seminal vesicles and testicles (15-17).

Prolactin serum levels have daily and circadian variations, its secretion is pulsatile, as described by Sassin et al, measuring blood levels every 20 minutes with raises up to 50% (13).

It shows a circadian rhythm with increases or secretory peaks during the sleep, started between 10 minutes and one hour after sleep beginning and reaching the highest values mainly in the deepest stages. These values do not go down in the next two hours after waking up and decrease slowly by the end of the afternoon, without any tendency to be repeated in the same individual in the days after, once in circulation prolactin mean life is estimated around 14 minutes.

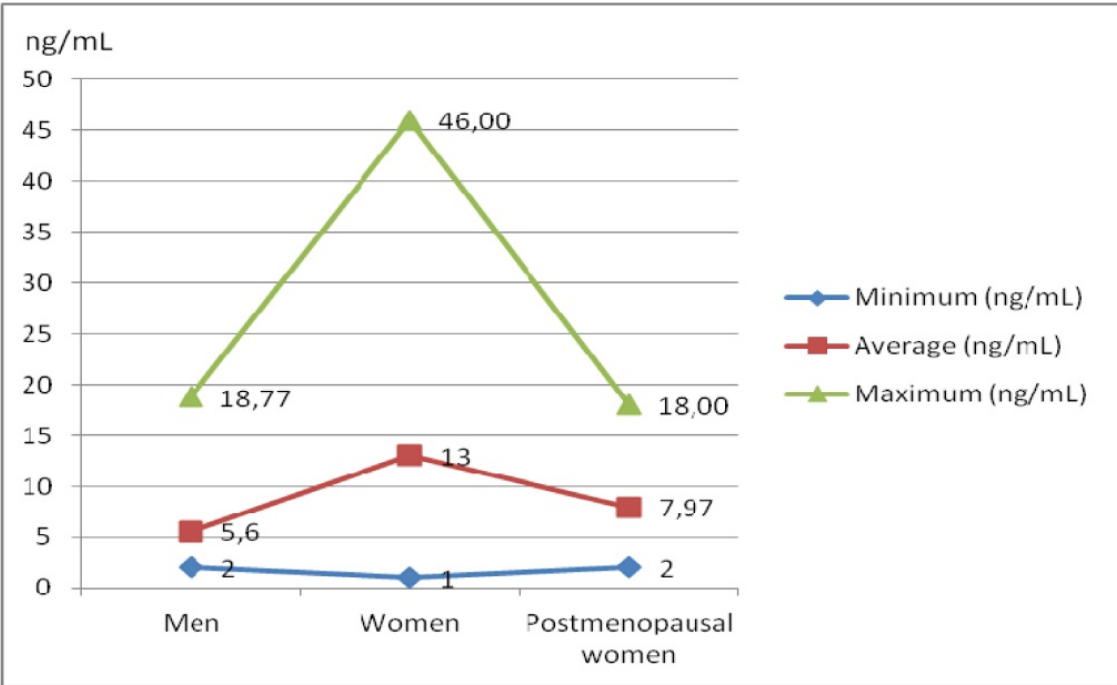
It seems that variation during time and sleep are due to the hypothalamus dopaminergic stimulus modifications, the circadian fluctuation is not affected by the use of oral contraceptives (10-15).

3. Limits of reference

In blood, prolactin can be found from the 16th week of fetal life, increasing its levels due to active secretion, as in birth it shows higher amounts to the ones recorded in the mother.

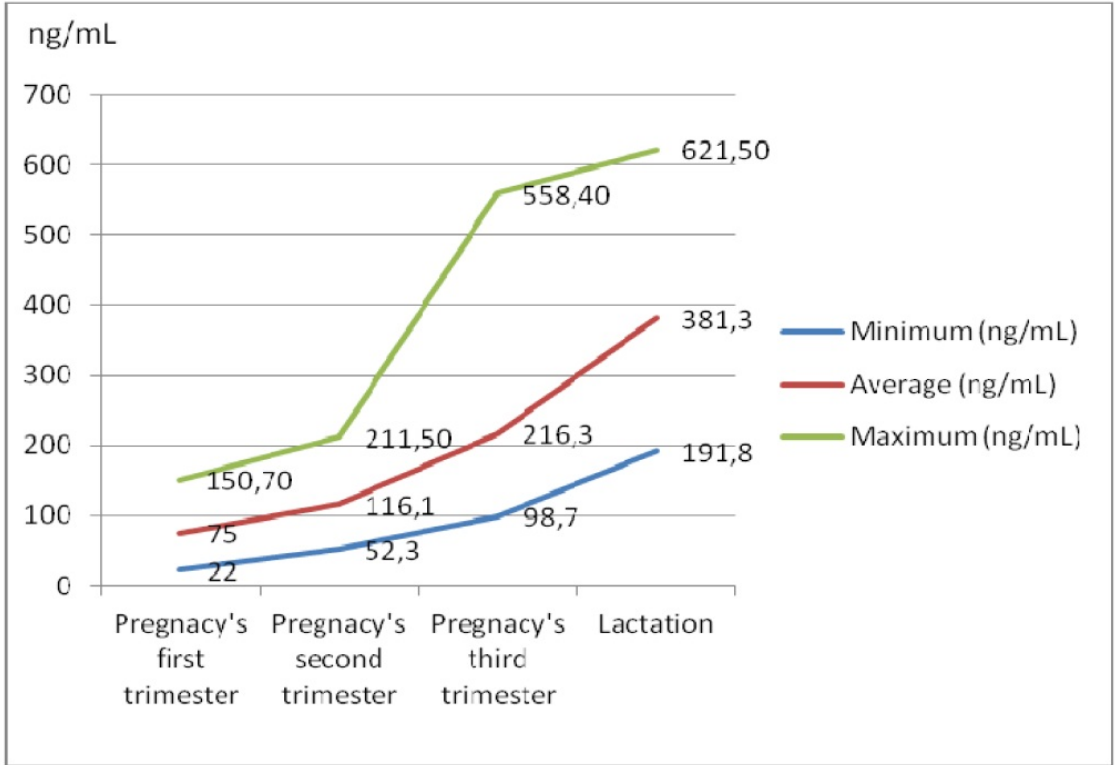
The normal described limits (figure 4 y 5) for healthy population are the following:

- Men: 2 - 18 ng/mL
- Non-pregnant women: 1 - 46 ng/mL
- Pregnant women: 35 - 600 ng/mL



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Figure 4. Prolactin’s limits of reference (I)



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Figure 5. Prolactin’s limits of reference (II)

The limits of reference change according to the studied population showing very pronounced individual variations, even in age and sex groups.

In fertile women the levels show a light elevation during ovulation and the luteinic phase, concerning to the follicular phase, corresponding to the endogenous estrogens liberated by the ovaries, which reduce the prolactin inhibitory factor in the hypothalamus increasing the amount of lactotroph cells as demonstrated in rats by stimulation although that effect depends on the dose and duration of the application, but it used to be shown by 24 hours (3, 12-15).

In postmenopausal woman and elderly men, levels go down, it is not clear if it is due pituitary deficiency or gonadal insufficiency, showing some role in gonadal function and aging.

The presence of different nonspecific stimulus, as the coitus, exercises, stress situations as surgery, insulin hypoglycemia course....can cause variations in prolactin secretion, some of the can have an adaptive nature, as them one occurred in hypoglycemia (12).

Because of what we mentioned previously, it is recommended to take from 2 to 3 samples to determine the prolactin level after 9 am to avoid late effects at night and hypoglycemia.

4. Hyperprolactinemia

As it has been described before, prolactin is secreted by lactotroph cells from the anterior hypophysis and it is subjected to the dopamine inhibitory effect in the hypothalamus. Any cause which interferes in its synthesis, the transport to the pituitary gland or the action over the dopamine receptors can produce hyperprolactinemia (Table 1).

Physiological Pregnancy and lactation Breast stimulation Stress
Hypothalamic diseases Craniopharyngioma Meningioma Dysgerminoma Sarcoidosis Eosinophilic granuloma Irradiation Vascular causes Pituitary stalk section
Pituitary pathology Prolactinoma Acromegaly Nonsecretory pituitary adenoma

Empty-sella syndrome Cushing disease Lymphocytic hypophysitis
Drugs Estrogens Antipsychotics: phenothiazine (chlorpromazine, perphenazine, fluphenazine, thorazine, promazine, fluoperazine, trifluoperazine, etc.), haloperidol, butyrophenone. Other dopaminergic blockers: metoclopramide, sulpiride, domperidone, cisperidone, cisapride. Antidepressant: monoamine oxidase inhibitors (imipramine), amoxapine, Tricyclic antidepressants. Antihypertensives: reserpine, methyldopa. Verapamil Fluoxetine Protease inhibitors Opiates: cocaine, morphine, heroine. Benzodiazepine Cimetidine (iv) Beta endorphins GABA Serotonin Noradrenaline HRT Adrenergic receptor antagonists (medroxalol)
Neurogenic causes Thoracic wall lesions Spinal cord lesions Breast stimulation
Other Primary hypothyroidism Chronic renal insufficiency Liver cirrhosis Suprarenal insufficiency Polycystic ovary syndrome Convulsions Idiopathic macroprolactinemia

GABA: Gamma-aminobutyric acid
HRT: Hormone replacement therapy
Iv: intra-venous

Table 1. Hyperprolactinemia causes

The most important cause of hyperprolactinemia is the secretory pituitary adenoma. Nevertheless, the most common cause are drugs and, when it is possible, the serum prolactin determination should be done once those are suspended.

5. Physiological causes

1. Pregnancy

Serum prolactin rises in a progressive way during gestation, but in a variable manner (18-19). At the end, the mean value is around 200 ng/ml but the range is 35-600.

Around the 6th week from the labor the normoprolactinemia is restored. Although the prolactin concentration is high before the labor, the milk secretion only takes place after it, because the high presence of estrogens and progesterone in pregnant women has an inhibitory effect over the milk secretion. When these hormones levels drop after the labor, lactation is produced.

During gestation the prolactin levels in the amniotic liquid can reach the 1000 ng/ml, higher concentration than any other organic fluid, this happens around the 15th and the 20th week of gestation and it drops slowly until the end of the pregnancy to 450 ng/ml. It is supposed to be produced by the fetal and the mother's hypophysis, with a possible function of fetal osmoregulation to survive in the intrauterine liquid environment, helping and contributing to the pulmonary maturing raising the content of phospholipids and changes in the lecithin-sphingomyelin ratio (20).

2. Breast stimulation

Nipple suction, probably by neural via, during breastfeeding, rises the serum values of prolactin, especially in the first weeks after giving birth in direct relation to the lactotroph hypertrophy by the estrogenic stimulus of the pregnancy (18-20)

3. Stress

Any kind of stress, physical or psychical, can cause hyperprolactinemia, which is normally slight, and rarely over 40 ng/ml.

4. Sexual contact

There is a dopamine decreasing after orgasm, immediately, the prolactin rises, in men and women, acting as a sexual satiation mechanism (21). In men, without any doubt contributes to the "turn around and snore" phenomenon. In women, its effects can be delayed.

Kruger TH et al have demonstrated that sexual intercourse with orgasm induced not only the well-established immediate prolactin increasing of 300% but also an additional prolactin elevation around noon of the next day. These fluctuations were measured on top of regular circadian rhythm (22).

6. Pathological causes

Pathological hyperprolactinemia can be caused by: lactotroph hyperplasia, lactotroph cells adenoma (prolactinoma) and miscellaneous.

1. Lactotroph hyperplasia

Lactotroph hyperplasia derives, in most cases, from the decrease of the dopamine inhibitory tone over the lactotroph cells. Hypothalamic and pituitary stalk lesions can cause light or moderated hyperprolactinemia, normally less than 150 ng/ml (18-19, 23).

The most common cause of hyperprolactinemia are the drugs. Any substance that acts over the central nervous system can, potentially, change the prolactin serum levels. Generally, the serum prolactin concentration increase a few hours or days after the drug administration and it gets normal from 2 to 4 days after its suspension.

Drugs can be divided in two big groups: drugs that act over the hypothalamus altering the dopamine metabolism and the drugs that act directly over the hypophysis. These last ones are more powerful and its action mechanism is dopamine antagonist, displacing it from its receptor in the lactotroph cell. Examples of these are the metoclopramide, sulpiride and domperidone. The Antihypertensives as reserpine and methyldopa act in the hypothalamus. Cimetidine and similar substances stimulate the receptor H₂ and provoke the hyperprolactinemia.

The hyperprolactine grade depends on the drug, for example, haloperidol can provoke rises lower than 20 ng/ml, but the risperidone can raise it over 100 ng/ml (19).

Estrogens rise the prolactin secretion and explain the higher response of prolactin in women in the presence of the different physiological stimulus.

Besides, up to a 30% of the patients with polycystic ovary syndrome show a light hyperprolactinemia, and the treatment with dopaminergic agonists can, in some cases, normalize the menstrual cycle.

The primary hypothyroidism is associated with a slight increase of the prolactin serum concentration in a 40% of the patients, but values over 25 ng/ml appear in less of the 10% (19, 23).

2. Lactotroph cells adenoma: prolactinoma

It is the most frequent secretory pituitary tumor and it represents a 60% of the operating tumors. The 90% of the prolactinomas are intrasellar microadenomas (<10 mm).

In women, over 90% are microadenomas, especially between 20 and 40 years old (2, 3). In male, the 60% are macroadenomas and it is because the poor symptoms, the delay of the medical visit for erectile dysfunction or a higher growth rate (19).

Prolactinomas are the most common pituitary tumors and they are, normally, benign. They are more frequent in women, but they can also appear in men. The symptoms that they cause, if the symptoms appear, are related to prolactin excess and so, the milk production in non-pregnant women, which is called galactorrhea.

Prolactinoma, the same as other pituitary neoplasms, comes from a monoclonal expansion of a cell that has mutated (18, 19, 23). It is usually sporadic and benign and it is rarely malign and metastatic.

Sometimes, it takes part of the type one multiple endocrine neoplasms (MEN). It is the only pituitary tumor with an effective medical treatment.

The prolactinoma natural history shows that over 90% of the microadenomas do not grow and they do not progress to macroadenomas, that suggest that these have a different biological behavior to the microadenomas (19, 24-27). Most of the times the lactotroph cells are the only ones affected but up to a 10% can alter, as well, the somatotropes or the mammosomatotropes, and a prolactin and growth hormone (GH) co-secretion is produced.

Prolactinoma can lead to:

- Interruption of the pulsatile secretion of the gonadotropin releasing hormone (GnRH) with inhibition of the gonadal steroids production and can provoke infertility and hypogonadism.
- Compression over adjacent structures.
- Deleterious effects over the organism, specifically the skeleton.

Prolactin secretion by the prolactinoma is characterized by:

1. Its efficiency: even small tumors, smaller than 1 cm, can produce significant hyperprolactinemia.
2. Its proportionality: usually, the prolactin serum concentration rises in direct relation to the adenoma size:
 - < 1cm is associated with serum prolactin values under 200 ng/ml.
 - Between 1 and 2 cm usually leads to values between 200 and 1000 ng/ml.
 - > 2 cm leads to prolactinemia over 1.000 ng/ml.

Discrepancies are frequent:

1. Big tumors with light hyperprolactinemia: they are usually atipic prolactinomas, worse differentiated and, so, less sensitive to therapy with dopaminergic agonists and more susceptible to surgical treatment.
2. Hook effect: very high levels of prolactin secreted by the macroadenoma saturate the assays and lead to an apparently low value (between 20 and 200 ng/ml), which could confuse the macroprolactinoma with a non-secretory macroadenoma. It is produced by interferences in the enzyme immunoassays for prolactin and it can be settled by serum dilution to 1:100, which will show the real prolactin serum values secreted by the tumor (19, 28-29).

7. Miscellaneous

1. Decrease of the prolactin clearing:
 - a. Chronic renal insufficiency. (CRI)

The hyperprolactinemia appears in most of the patients with CRI and dialysated. When these patients take medication that can alter the hypothalamic regulation of the

prolactin, this can take to serum values over 2000 ng/ml. It is produced by a decrease of the glomerular filter, although a pituitary primary defect associated to a renal failing cannot be dismissed.

b. Macroprolactinemia.

In some patients with hyperprolactinemia without a perceptible cause or idiopathic, this could be due to an excess of macromolecules of prolactin, known as macroprolactin or big prolactin. The macroprolactin is a complex of prolactin joined to an IgG antibody with a low bioactivity but with a higher mean life than normal prolactin, of 23 kDa, which condition its lower clearing and the consequent accumulation of high serum concentrations.

To distinguish it from other causes, some samples of serum with polyethylene glycol should be precipitated (13, 19-20).

This prolactin variety can be present in over 10% of the patients with hyperprolactinemia, and its presence should be suspected in every hyperprolactinemia without a defined etiology, with poor or nonexistent symptomatology, despite of the high prolactin serum concentrations and with poor or nonexistent response to normal therapy with dopaminergic agonists (13,19-20, 28-30).

This situation can lead to unsuitable diagnosis and treatments in patients with hyperprolactinemia, but usually without clinical significance. Every hyperprolactinemia assay should consider the possible presence of macroprolactinemia (19, 30).

When the cause is not found and the imaging tests are negative, the hyperprolactinemia is defined as idiopathic. In most of the cases they are small microadenomas. A 10% of them will be visible between 2 and 6 years. In other cases it is a transitory and self-limited disorder that can be solved spontaneously (19,31).

2. Hyperprolactinemia related to psychotropic drugs

Prolactin determinations will not be needed in individual under psychotropic treatment, but if there is indicative clinical symptoms of hyperprolactinemia.

However, in a patient with hyperprolactinemia under psychotropic drugs, among others, subsequent studies (hormonal and imaging) will be performed only if:

- There are clinical symptoms derived from hyperprolactinemia.
- There are prolactin serum concentrations over 6 times the normal value.

The assessment of the new patient should be done ideally 3 months after the medication suppression or, if not possible, the possibility of a substitutive medication that does not provoke hyperprolactinemia should be assessed, always under psychiatric control.

It is normally not recommended the dopaminergic agonists use in a combined form to psychotropic or dopaminergic antagonist drugs because of the undesirable effects. (19,20).

8. Assessment and diagnosis of the hyperprolactinemia

Because the secretion of the prolactin is pulsatile, it is advisable to determine the serum prolactin in, at least, 2 times or more.

To the most of the clinical laboratories, the normal serum concentration is less than 25 ng/ml in women and 20 ng/ml in men.

(Note: conversion factor: $\text{mU/l} \times 0,0472 = \text{ng/ml}$; $\text{ng/ml} \times 21,2 = \text{mU/l}$.)

The determination should be done, ideally, in a basal situation, under rest conditions and after suppression of any medication that can interfere in its quantification.

The clinical records are determinant to the hyperprolactinemia treatment:

- The data collection, especially about drugs, must be meticulous.
- Other non-pituitary causes should be dismissed: pregnancy, thyroid, renal, hepatic and adrenal dysfunction.
- We should investigate the existence of compressive symptomatology like cephalalgia, chiasmatic syndrome, liquorrhea and pituitary dysfunction data related to the pituitary tumor presence.

Values of serum prolactin can lead to the diagnosis (figure 6):

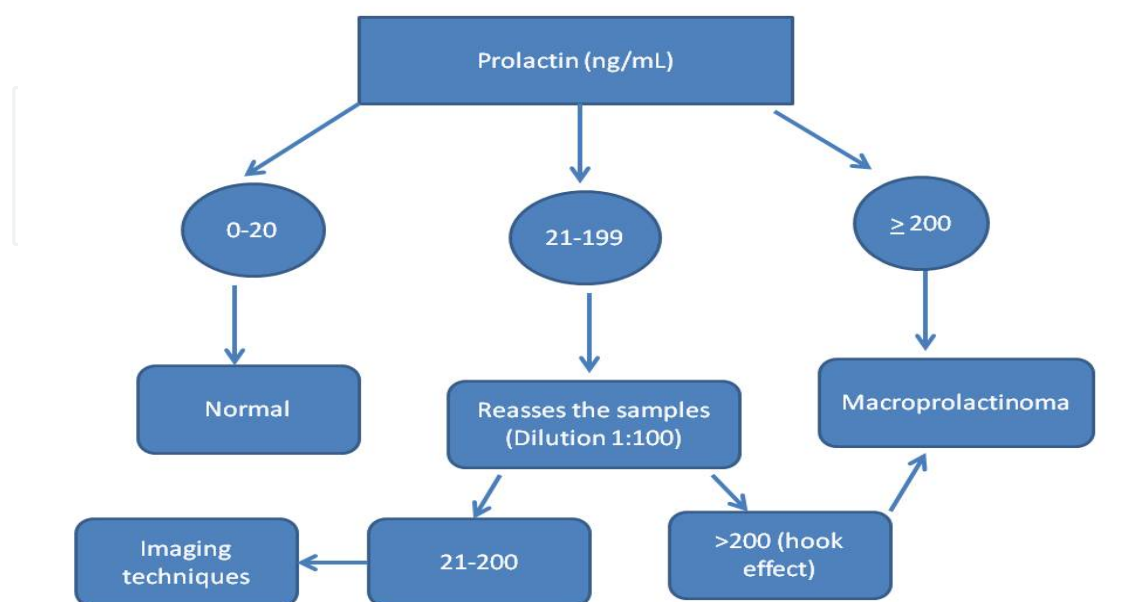
- Serum concentrations slightly raised (20-40 ng/ml) require confirmation before cataloguing the hyperprolactinemia state.
- Prolactin serum values between 20 and 200 ng/ml can appear in iatrogenic or extrapituitary hyperprolactinemia.
- Serum values between 40 and 100 ng/ml appear in secondary and idiopathic causes and less frequently in some microprolactinomas.
- Serum concentrations between 100 and 200 ng/ml, ruled out the pregnancy, are characteristic of a prolactinoma.
- Values over 200 ng/ml appear in macroprolactinomas.

It is convenient to insist in the importance of differentiate between the big pituitary non-secretory macroadenomas, that apply compression to the pituitary stalk and can curse with prolactin serum values that are not too high, generally lower than 200 ng/ml (pseudo-prolactinoma) from the real macroprolactinomas, which usually show prolactin serum concentrations over 200 ng/ml.

The first ones are susceptible of surgical treatment, while the prolactinomas are treated, most of them, with medical treatment. In a same way, low prolactin serum concentrations can coexist with uncovered small tumors in an incidental way, and they can lead to false diagnosis of microprolactinoma (19, 33).

Nevertheless, values between 20 and 200 ng/ml, in presence of a macro-lesion, obliged to reassess the samples using a dilution of 1:100 to dismiss the hook effect described previously and according to it very high values of serum prolactin saturate the assays and lead to an

apparently low value, that could confuse the macroprolactinoma with a non-secretory macroadenoma (31).



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Figure 6. Diagnosis of the hyperprolactinemia

The dynamic tools of suppression or stimulation of prolactin (TRH, L-dopa, etc.) offer inconsistent results and should be rejected (19). In the study of the pituitary gland functionalism, in the case of a microadenoma, the determination of the basal pituitary hormones would be normally enough.

On the other hand, the presence of a macroadenoma would make advisable a deepest anterior hypophysis study.

9. Protocol of samples extraction to determine the serum prolactin

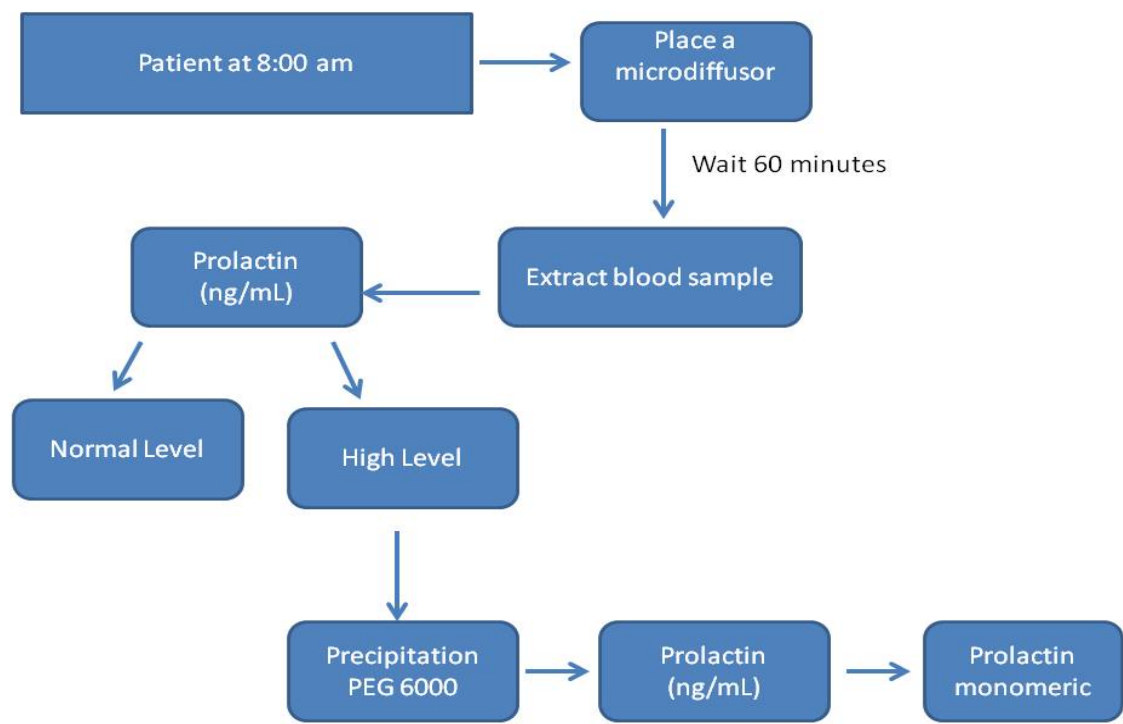
Prolactin measurement is subjected to a very careful extraction protocol, because most of the errors happen in the pre-analytic stage (between 53-75%) (20, 32).

Due to some physiological stimulus that rise prolactin levels, it is recommended to use 2-3 samples obtained at different times to assure that a patient suffers hyperprolactinemia (19-20).

Some clinical guides as the "Pituitary Society Guidelines" (35) recommend the macroprolactin screening under certain conditions (moderate increase of prolactin levels and the patient should not show typical symptoms associated to hyperprolactinemia). Other authors recommend the macroprolactin screening performing to all those samples that show high prolactin concentrations (19, 20, 36).

Our work team has developed a protocol to optimize the samples extraction and the monomeric prolactin measurement, when values are above the reference limits (19). This procedure has shown to reduce the amount of false hyperprolactinemias if compared to the direct puncture technique, because this eliminates the possible increase of prolactin due to stress puncture.

In our protocol (figure 7), patient visit us at 8.00 a.m., following the pre-analitic requirements for prolactin measurement (table 2). Then we place a micro-diffusor (canalizing the vein, which stays permeable, salinizing the blood vessel puncture). Once it has been 60 minutes since the micro-diffuser placement, we will extract the blood sample.



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Figure 7. Protocol of extraction samples to determine the serum prolactin

- Being awake 2 hours before extraction and without making any physical effort.
- Avoid high-protein diet from the day before the extraction
- Avoid high-fat diet from the day before the extraction.
- Avoid breast stimulation from the day before the extraction.
- Be 8-10 hours of fasting prior to extraction.
- Do not take medications that may increase or decrease prolactin.
- Be relaxed and rested for at least 30 min before extraction.
- Do not be under stress.

Table 2. Conditions for the extraction of prolactin

The monomeric fraction determination was performed when we found high prolactin levels after 60 minutes, then we perform the macroprolactin precipitation through PEG 6000 (20, 36)

Polyethylene glycol was mixed in equal parts with the patient serum, then it was stirred and centrifuged. Prolactin was measured in the supernatant (monomeric prolactin).

We show in our report the prolactin measure at 60 minutes, the percentage of recuperation after precipitation with PEG 6000 and the monomeric prolactin (we add in a note this is the fraction that has biological activity).

10. Imaging techniques

Neuro-imaging studies must be performed with any hyperprolactinemia degree that cannot be explained with the purpose of dismiss the hypothalamic-pituitary disease.

The Magnetic resonance imaging (MRI) with gadolinium gives the most precise anatomical details, and let us measure the tumor size and its relation to the optical chiasma and the cavernosus sinus, that is why this is, nowadays, the best imaging technique (19, 32). If MRI is normal, after excluding other hyperprolactinemia causes, we should talk about idiopathic hyperprolactinemia.

Computed tomography with intravenous contrast is less efficient than MRI in small adenomas diagnosis and the definition of big tumors, but it can be used if MRI cannot be used or if it is contraindicated. The rest of the image techniques that are more usual like X-Rays and isotope techniques are not recommended. (37).

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