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Review Article

PROLACTIN AND HYPERPROLACTINAEMIA IN FEMALE REPRODUCTIVE ENDOCRINOLOGY – AN UPDATE

Ranko M. Kutlešić[1,2], Jasmina Popović[1,2], Milan Stefanović[1,2], Predrag Vukomanović[1,2], Jelena Milošević Stevanović[1,2], Danka Mostić Stanišić[3]

[1]Clinic of Gynaecologyand Obstetrics, Clinical Centre Niš, Niš, Serbia
[2]Faculty of Medicine University of Niš, Niš, Serbia
[3]Institute of Gynaecology and Obstetrics Belgrade, Clinical Centre of Serbia, Belgrade, Serbia

Abstract. *Hyperprolactinaemia is one of the most frequent causes of anovulation, resulting in infertility and hypoestrogenic state with consequences on overall women's health. Recent investigations on biological actions of prolactin, especially prolactin of extrapituitary origin, expand our knowledge on prolactin role in the human organism and open new questions connected with female reproductive function and treatment of female infertility. This article represents the review of current knowledge on prolactin physiology, etiopathogenesis, clinical features, assessment , differential diagnosis ,and teatment of hyperprolactinaemia in the female patient.*

Key words: *prolactin, hyperprolactinaemia, physiology, female infertility, treatment.*

Introduction

Prolactin (PRL) was first discovered in the late 1920s by different authors who demonstrated the ability of the injected bovine pituitary extract to cause lactation in rabbits [1].

The hormone was purified in 1932 by Riddle et al. and was named "pro-lactin" due to its it's lactogenic action [2].

PRL was not able to be separated from growth hormone (GH) till 1970's when adequate radioimmunoassay was developed by Friesen et al [3, 4].

Today, PRL is known to act at many different tissues with numerous biological activities. Hyperprolactinaemia is one of the most common problems in human endocrinology, especially connected with reproduction. In fact, PRL is viewed as a hormone on a global level, but its paracrine/autocrine action as cytokine is also the subject of numerous investigations.

Physiology of PRL Secretion

PRL belongs to the PRL/GH/placental lactogen family. Those hormones share a similar structure, function, and binding properties, as well as the origin from a common ancestral gene from which they have diverged 400 million years ago [5].

The prolactin gen is located on chromosome 6 in the human genome [6], with different promoter regions directing pituitary and extrapituitary PRL synthesis, which is the unique characteristic of humans [7].

Correspondence to: Ranko Kutlešić M.D., Ph.D.
Faculty of Medicine, Niš, Dr. Zorana Djindjića Blvd. 81,
18000 Niš, Serbia
E-mail: mkutlesic5@gmail.com
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This gene is encoding prohormone for prolactin, which is consisted of 227 amino acids, with a signaling peptide of 28 amino acids. PRL is a polypeptide hormone, aminoacid chain consisting of 199 amino acids, 50% of them are in the form of α-helix and the rest forms the loop. The tertiary structure was predicted according to the current three-dimensional model: prolactin contains four long α-helices, arranged in antiparallel fashion [5, 8].

The molecular weight of PRL is around 23 kDa, which represents the main and biologically the most potent form of PRL in circulation - monomeric or *small* PRL. There are also the variants of PRL molecule: 60 kDa form – *big PRL* (dimmer) and *big-big PRL* of 150 – 170 kDa. Posttranslational processing is taking place in the anterior pituitary, including polymerization, phosphorization, glycolysis as well as formatting complexes with immunoglobulins (the most often with IgG in humans) or forming covalent and noncovalent bonds [5]. Such macromolecular forms have clinical implications, which will be discussed later.

PRL may have pituitary and extra-pituitary origin. The main sources of prolactin in humans are anterior pituitary lactotrophs. Synthesis and secretion of pituitary PRL are regulated by both inhibiting, and releasing factors (Table 1). Inhibiting factors include dopamine, gamma-aminobutyric acid (GABA) and somatostatin [5]. Hypothalamic dopamine is considered to be the main prolactin inhibiting factor in humans exerting its action through D2 and D4 receptors located on cell membranes of lactotrophs. Such dopamine action results in down-regulation of PRL gene expression reduced PRL secretion and decreased lactotroph proliferation [9].

Different molecules release pituitary prolactin (table 1), thyrotropin-releasing hormone (TRH) being clinically the most important, but "PRL-releasing factor" has not been identified as it is the case for other pituitary hormones [10].

Table 1 PRL inhibiting and releasing factors

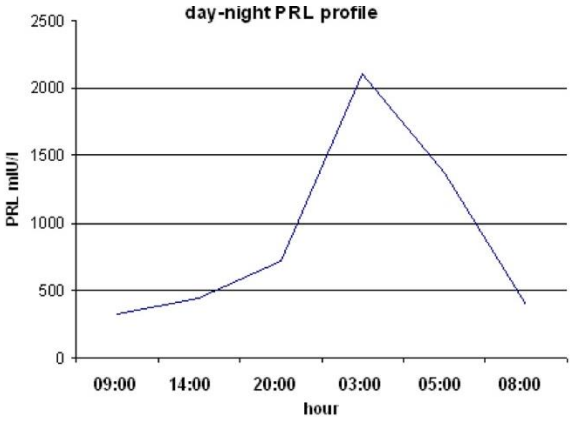
PRL inhibiting factors	
dopamine from hypothalamus	
gamma-aminobutyric acid (GABA)	
somatostatin	
PRL releasing factors	
thyrotropin-releasing hormone (TRH)	vasoactive intestinal polypeptide (VIP)
endogenous opioides	neurotensin
oxytocin	galanin
vasopressin	salsolino
serotonin	
Physiological "PRL-releasing factor"?	

Pituitary PRL is secreted in a pulsatile fashion, with peaks 20–30 minutes apart. This fact has clinical implications: taking three samples in 20–30 min. apart could help to make the correct diagnosis of hyperprolactinaemia.

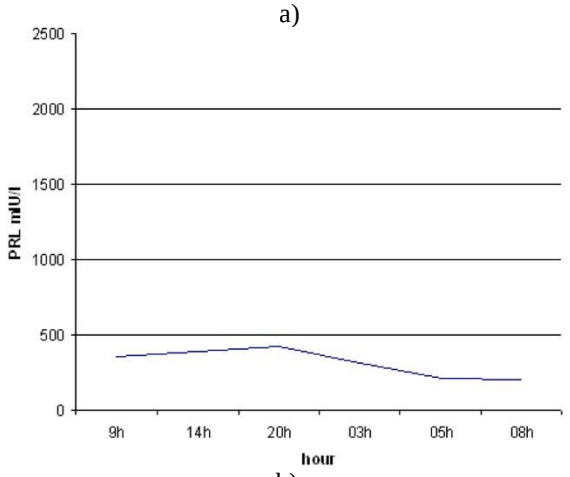
Pituitary prolactin secretion is characterized by a unique circadian rhythm. Higher levels occur during the sleep, with two peaks: around 17-20h and higher one between 02h and 04 h (about 4–5 hours after the beginning of the sleep). These facts also have clinical implications: higher PRL levels during the sleep cause "nocturnal hyperprolactinaemia" and possible galactorrhoea, especially in chronic stress (Figure 1).

PRL serum levels in humans are also fluctuating during the menstrual cycle, increasing during the follicular phase with periovulatory peak [12], so it was recommended to measure PRL serum levels in the early follicular phase, as we do in our everyday clinical practice [13].

Extra-pituitary prolactin is structurally identical to pituitary PRL. It is produced in the ovaries, uterus and endometrium, breast, prostate, lymphocytes, haematopoetic cells, adipose tissue, skin, thymus, lymphatic system, endothelium, and the brain. The action is still under investigation, the most probably autocrine/paracrine nature, but it was well established that its regulation is site- specific and quite different from the pituitary PRL [5, 14].



a)



b)

Fig. 1 Day and night profile of PRL serum levels in our patient with so-called "normoprolactinaemic galactorrhoea" caused by nocturnal hyperprolactinaemia due to chronic stress (being refuge during the civil war). Morning PRL levels are within physiological limits, while nocturnal PRL serum levels are higher than normal (a). Galactorrhoea and nocturnal hyperprolactinaemia ceased after the normalization of the living conditions (b) [11].

Actions of PRL

PRL acts through its receptor (PRL-R): a single membrane- bound protein of the cytokine receptor family, expressed in the pituitary and in the numerous other tissues as the mammary gland, endometrium, ovaries, heart, lung, thymus, liver, pancreas, spleen adrenal gland, skeletal muscle, bone (osteoblasts), skin, and brain [5].

PRL has more than 80 functions and over 300 separate biological activities, the most investigated are reproductive and homeostatic activities [5].

Reproductive action of PRL includes roles in mammogenesis, lactogenesis, and galactopoiesis (development and maturation of the breast during pregnancy, induction, and maintaining of lactation) as well as its role in follicular development and maintenance of the *corpus luteum* (luteotropic action of *physiological* levels of PRL) [15]. PRL is also involved in oogenesis and adequate implantation [15].

The possible PRL role in spermatogenesis is supported by findings of male infertility in knock-out PRL-R mice [9, 16].

The reproductive role of PRL is connected to its action as brain neuropeptide: animal experiments showed that reproductive behaviour was under the influence of PRL, which could stimulate sexual receptivity during the estrus [17], while inhibited sexual behaviour during the lactation [18].

As brain neuropeptide, PRL also has a role in mediating the positive influence of social interactions between mother and child or between mating partners on the mental and physical state and beneficial effects of such interactions on adaptive processes related to emotional and physiological stress coping in both sexes [19].

PRL is also known as "stress hormone": increases secretion of ACTH, induces adrenal hypertrophy and storage of cholesterol esters, and stimulates the secretion of androgens (inclouding DHEA), cortisol, and aldosterone in adrenals [12].

Extrapituitary PRL acts as a cytokine on numerous sites. PRL produced by lymphocytes and haematpoietic cells is supposed to be involved in the immune response to stress [5, 12, 14, 20].

PRL promotes bone growth and mineralization in foetus, whereas it is involved in bone resorption in pregnancy, providing micronutrients to foetus [21].

PRL has vasoconstrictive action and a possible role in the development of pre-eclampsia or peripartal cardiomyopathy [15].

During the pregnancy, PRL is supposed to be included in fetal osmoregulation and inhibiting water transport across the human amnion [22].

Numerous actions of the extrapituitary PRL are still under investigation. The PRL roles in human physiology are illustrated in the best way by the following words [5]: *"It has been well recognized that prolactin ensures survival of the species through its reproductive role and survival of the individuals of the species in its homeostatic roles. While we know a great deal about the chemistry, biological actions, and controls in its reproductive role, there is a paucity of similar information in its homeostatic roles".*

Etiopathogenesis of Hyperprolactinaemia

Hyperprolactinaemia could be physiological, pathological, and iatrogenic. The main causes of hyperprolactinaemia are listed in the Table 2.

Physiological causes could elevate PRL synthesis and release in different manners.

Endogenous oestrogens enhance PRL secretion by regulation of PRL gene expression, downregulation of dopamine receptor expression, and stimulation of lactotroph cell hyperplasia [5].

During the pregnancy PRL serum levels progressively rises to 4 000 – 10 000 mIU/l (200 – 500 ng/ml) [23].

Suckling – induced PRL release during breastfeeding is caused by lowered dopamine tonus, but PRL releasing factors as TRH, oxytocin, etc (Table 1) are also proposed to be involved [5, 24].

Neural mechanisms interfering with dopamine transmission are involved in PRL release during the suckling in lactation and nipple stimulation [5], which is not observed during the breast examination, breast ultrasound, or mammography. [25-27].

Table 2 Etiology of hyperprolactinaemia

Physiological hyperpoalctinaemia:
- pregnancy, puerperium and lactation, stress (psychic, physic, surgery and anaesthesia, hypoglicaemia etc), during the sleep, nipple stimulation and coitus, exercises and in 2.5% of healthy people,

Pathological hyperpolactinaemia:
- prolactinomas, other pituitary adenomas, and pituitary conditions (acromegaly, hypophysitis, macroprolactinaemia etc)
- hypothalamic conditions and pituitary stalk compression (tumours, granulomas, infiltrative lesions, tuberculosis, sarcoidosis, cranial irradiation, trauma with stalk section, Rathke cleft cyst, craniopharyngiomas etc)
- idiopathic hyperprolactinaemia
- chronic renal failure
- hypothyroidism
- hepatic failure
- chest: neurogenic chest wall trauma, surgery scars, herpes zoster
- epileptic seizures
- autoimmune diseases
- 6-pyruvoyl tetrahydropterin synthase deficiency
- ectopic PRL production by different tumours

Pharmacological hyperprolactinaemia:
- dopamine receptor antagonists and dopamine synthesis inhibitors
- dopamine depleting agents (antihypertensives: methyl dopa, reserpine, verapamil, etc)
- hormones and neuropeptides – stimulators of prolactin release (TRH, estrogens – oral contraceptives, etc)
- opiates and opiate antagonists, morphine derivatives, aesthetics, opium smoking, opioid addiction, cocaine and marijuana
- antihistamines H2 (cimetidine, meclizine, etc)
- antipsychotics / neuroleptics, antidepressants, anticonvulsants,
- antiemmetics (domperidone and metoclopramide)
- cholinergic agonist
- catecholamine depletor

Oral contraceptives containing high doses of oestrogen (>= 35 mcg) could rise PRL serum levels by alteration of dopamine regulation [28], which is not a case with modern contraceptives with lower amounts of oestrogen [29].

Stress-induced changes in dopamine and serotonin may affect PRL release causing hyperprolactinaemia [20]

It was already mentioned that hypothalamic dopamine acts through D2 receptors on lactotrophs as the main PRL inhibiting factor. Therefore, the main reasons for elevated serum PRL levels in pathological and pharmacological could be as follows:

- high PRL production (by prolactinoma),
- disruption of the dopamine transport to the pituitary (due to stalk compression by tumours or inflammation),
- decreased dopamine PRL inhibition and elevated estrogen levels in hepatic failure,
- decreased PRL clearance and increased PRL secretion in renal failure,
- blockade of endogenous dopamine receptors by a variety of drugs,
- PRL synthesis stimulated by medications.

Clinical Features of Hyperprolactinaemia

Hyperprolactinaemia causes hypogonadism in women and men. Syndrome "galactorrhoea – amenorrhoea" was first described by Hypocrite. Women with hyperprolactinaemia could experience cycle irregularity (amenorrhoea and oligomenorrhoea) or even to have regular cycles, but the consequence is infertility in the most. In fact, hyperprolactinaemia disturbed ovulation in women: on one end of the spectrum of the ovulation disorders caused by hyperprolactinaemia is amenorrhoea due to complete anovulation; on another end of the spectrum is luteal phase deficiency in women with almost regular cycles, but still with the problem to conceive.

Hyperprolactinaemia in women could cause the development of the hypoestrogenic state resulting in osteoporosis. In fact, hyperprolactinaemia could increase bone resorption and inhibits bone formation, both in men and women [30].

Such hypoestrogenemic state is also associated with multiple impairement of female sexual functions (sexual desire and arousal, lubrication, orgasm, sexual satisfaction, and dyspareunia) [31].

Galactorrhoea is present in 10% to 90% of hyperprolactinaemic women and in 14 – 33% of men [32]. Nipple discharge could be colorless, yellowish, white like breast milk in lactation or even dark. "Normoprolactinaemic galactorrhoea" is a condition characterized by galactorrhoea associated with normal PRL serum levels measured in usual fashion. Nocturnal hyperprolactinaemia is a possible reason for that condition, for diagnostic purposes day-night prolactin profile should be obtained (Figure 1).

Hyperandogenemia could be present in 25% of hyperprolactinaemic women, due to the increase in adrenal DHEA, the consequence is mild hirsutism. Hyperandrogenemia could be also present in patients with prolactinomas [33].

The connection between hyperprolactinaemia and female pattern hair loss is still unclear [34], but we have seen such cases in our own clinical practice.

In men, hyperprolactinaemia causes hypogonadism: impotency, loss of libido ,and gynecomastia. Anaemia, decreased energy and muscle mass may be also present as secondary manifestations of hypogonadism [35, 36].

Abnormal pituitary findings were found in 50-80% of patients with monomeric hyperprolactinaemia [37]. Prolactinomas are the main causes of hyperpolactinaemia and the most common type of pituitary adenomas (about 40%) [38].

In patients with prolactinomas, neurological manifestations are present in cases with macroprolactinomas (pituitary adenoma > 10 mm in diameter): visual disturbances if the tumor compresses optical chiasma, which is not the case with microprolactinoma (pituitary adenoma < 10 mm in diameter).

The existence of hyperprolactinaemia was reported in numerous autoimmune disorders including: systemic lupus erythematosus, rheumatoid arthritis, sclerodermia etc, which is explained by immunomodulatory effects of PRL acting as cytokine on the level of T- and B-lymphocytes, enhancing inflammatory response and immunoglobulin production [39].

Hyperprolactinaemia has a negative influence on glycoregulation, it was demonstrated that hyperpolactinaemia in patients with prolactinoma was associated with a higher risk of hyperglycaemia accompanied by obesity. Bromocriptine and cabergoline have favorable effects on glucose metabolism, but the exact mechanism of its action on glycemic control and favorable cardio-metabolic profile is still unclear and it seems to be that this action is more complex than "the historical explanation of "resetting" the circadian clock" [40].

Metabolic consequences of dopamine agonists treatment for hyperprolactinaemia were investigated in 14 consecutive patients with prolactinoma: insulin sensitivity tended to improve after 6 months of the treatment with dopamine agonists (bromocriptine and cabergoline) [41].

It was recommended that hyperprolactinaemic premenopausal women with abnormal lipide profile and positive familial history of coronary disease, should be subjects of investigation for hyperinsulinaemia, and if it exists, PRL serum levels and insulin resistance should be normalized by adequate therapy [42].

Hyperprolactinaemia is also associated with endothelial dysfunction, development of perimenopausal atherosclerosis, and risk for cardiovascular disease, probably connected with vasoconstrictive characteristics of prolactin, but further studies are needed for definitive conclusions [43].

Osteoporosis could be developed in a hyperprolactnaemic patient due to hypoestrogenemic state and decreased osteocalcin levels [44].

It was also hypothesised that multiple pregnancies and iatrogenic hyperpolactinaemia could increase the risk for otosclerosis [45].

Hyperprolactinaemia and Female Infertility

Hyperprolactinaemia causes anovulation and infertility. High PRL levels suppress GnRH (via reduction of kisspeptins) and decrease LH pulse, ovarian oestrogens, and progesterone production [46, 47]. The consequences are menstrual irregularities (amenorrhoea or oligomenorrhoea), infertility, decreased libido, and galactorrhoea [38, 46].

A novel hypothesis states that kisspeptin could be of crucial importance for the explanation of anovulation and infertility in hyperpolactinaemic state [48-50]. Kisspeptins, neuropeptides encoded by KISS1 gene, are potent stimulators of GnRH neurons and important for pubertal maturation and regulation of reproduction [50]. Kisspeptin is expressed in hypothalamic arcuate and anteroventral periventricular nuclei. In the hyperprolactinaemic mouse model with continuous infusion of prolactin subcutaneously, the kisspeptin content was reduced and administration of kisspeptin intraperitoneal injection once daily for 20 days restored estrous cyclicity, induced ovulation, and increased LH and FSH levels in circulation [51]. Nevertheless, kisspeptins are not recommended for the therapy of amenorrhoea [52].

Kisspeptin administered in brain chambers
↓
Activity of tuberoinfudibular DA neurons are modulated
↓
DA tonus decreases
↓
PRL increases

Scheme 1 Influence of kisspeptin on PRL release [53]

Hyperprolactinaemia inhibits expression of kisspeptins
↓
Kisspeptin decreases
↓
Stimulation of GnRH neurons is absent
↓
Anovulation

Scheme 2 Influence of PRL on GnRH production [48, 50, 54].

In the human ovary hyperprolactinaemia inhibits development of corpus luteum, granulose cell luteinization, and steroidogenesis. PRL serum levels higher than 2000 mIU/l (about 100 ng/ml) inhibit progesterone secretion [55, 56].

Women with PCOS have elevated PRL serum levels in 30% of cases, thought to be a consequence of elevated estrogen levels and reduction of dopamine tonus [57].

However, the relationship between PCOS and hyperprolactinaemia remains unclear. Some authors stated that PCOS and hyperprolactinaemia are distinct entities [58, 59].

Hyperprolactinaemia is reported to be present in patients with endometriosis, moreover, there was a positive correlation of serum prolactin levels and stadium of endometriosis [60, 61].

Patients with endometriosis have exgaggerated nocturnal PRL secretion, it was stated *"this is the part of pathophysiology of that disease"* [62]. Human decidua produces prolactin and prolactin receptors are found in endometriotic tissue, therefore, it was postulated that the patients with endometriosis have at least occult hyperprolactinaemia according to TRH (thyrotropin -releasing hormone) stimulation, with higher serum prolactin levels in patients who had not achieved pregnancy during the treatment for endometriosis [63-65].

On the other side, there are reports denying the connection of prolactin with endometriosis [66, 67].

The influence of prolactin on fertility depends on serum concentrations: as the level of prolactin increases, cycle abnormalities can progress sequentially from an inadequate luteal phase to intermittent anovulation with oligomenorrhoea to total anovulation and amenorrhoea. The consequence is infertility; therefore, it is crucial to control prolactin levels in hyperpolactinaemic infertile patients.

Hyperprolactinaemia and Pregnancy

It was reported that up to one- third of hyperolactinaemic patients achieved pregnancy in unstimulated cycles, though it must be noted that most of the studies on that issue were conducted before the introduction of macroprolactin screening in routine clinical practice. Nevertheless, during the pregnancy of previous hyperprolactinaemic patients, there is no increased percentage of spontaneous abortions, nor increased perinatal mortality and morbidity. Breastfeeding is also allowed. There are no proven harmful effects of dopamine agonists as bromocriptine and quinagolide, including teratogen effects and effects on fetal osmoregulation. It was recommended that dopamine agonist therapy should be stopped when pregnancy is diagnosed [38].

Another concern during the pregnancy is a possible increase of the size of prolactinomas. The rise of microprolactinomas is extremely rare during the pregnancy: in 5% of all cases is asymptomatic, only in 2% of pregnant women the rising microprolactinoma could cause headache or visual disturbances [68, 69].

Macroprolactinomas rise more often: 15% of pregnant women with macroprolactinomas have symptoms due to increased tumour: headache and visual disturbances [69, 70, 71]. In such cases, it is possible to use NMR for diagnosing and commence the therapy with dopamine agonists which could control the rise of the tumour in most of the patients [72, 73]. It is recommended that during the pregnancy follow-up should be based on the occurrence of the symptoms: NMR of the pituitary sella should be done in case of the appearance of the symptoms. Routine measurements of the PRL serum levels during the pregnancy are not necessary [38].

A rare, but serious complication of the prolactinoma during the pregnancy is tumour necrosis and bleeding inside of the tumour, resulting in insipid diabetes and pituitary insufficiency after the delivery [70].

Clinical experience showed that some previously hyperprolactinaemic patients after the delivery have normalized PRL serum levels and commenced spontaneous menstrual cycles without therapy, moreover get pregnant spontaneously, even they had many problems achieving the first pregnancy. This is explained by spontaneous tumor necrosis during the pregnancy or sponatneous recovering of the primary dysfunction related to hyperprolactinaemia [74-76].

Diagnostic Evaluation of Hyperprolactinaemia

The diagnosis of hyperprolactinaemia is established by single measurements of serum PRL levels in two separated occasions (with serum sampling at least two hours apart from sleeping or eating). The serum should be obtained without excessive venipuncture stress and a level higher than the upper limit confirmed the diagnosis (> 530 mIU/l - according to World Health Organization Standard 84/500), as it was recommended previously [38, 77, 78].

When the obtained level of prolactin raised any doubt, the sampling should be repeated on another day at 15–20 min intervals to avoid prolactin pulsatile secretion.

PRL serum levels higher than 250 ng/ml are suggestive of the presence of a macroprolactinoma. PRL levels <100 ng/ml are associated with pseudoprolactinomas, drug-induced hyperprolactinaemia or systemic disease [79], but this is not always the rule [80, 81].

In cases of highly elevated PRL serum levels "hook effect" should be considered, therefore PRL serum levels should be measured in diluted blood serum. Clinically, such cases are present with symptoms of hyperprolactinaemia and falsely low PRL serum levels in undiluted spacemen [82, 83].

Diagnostic evaluation of hyperprolactinaemia includes: medical history, physical examination, assessing the clinical features and laboratory findings (especially PRL serum levels), as well as imaging studies of the pituitary and sella turcica (preferably pituitary NMR). Screening for macroprolactinaemia is also desirable, in asymptomatic patients is highly recommended [38].

Taking a proper medical history is essential in cases of pharmacological hyperprolactinaemia, but the concomitance of a pathologic cause should be always kept in mind. PRL measurements should be repeated after the discontinuation of the medication after 3 to 4 days (corroborated by a psychiatrist). If the discontinuing of the medication is not possible, pituitary NMR should be performed. In cases of confirmed drug-induced hyperpolactinaemia, the alternative medication should be tried, if possible [38, 84].

A similar situation is in the case of the rare concomitance of primary hypothyroidism and prolactinomas, which should be suspected when high PRL serum levels persist despite normalization of thyroid function [80].

Macroprolactinaemia

In the case of obvious discrepancy between high PRL serum levels and the absence of clinical symptoms and signs of hyperprolactinaemia, macroprolactinaemia should be suspected.

Macroprolactinaemia is a condition where 60% of circulating PRL is made of macroprolactin, form of circulating PRL with lesser biological activity.

In patients with hyperprolactinaemia about 25% have macroprolactinaemia (ranges from 10% to 35%) [85-89] but the precise prevalence of macroprolactinaemia in hyperprolactinaemic and the general population is still unknown [90].

The gold standard for diagnosing macroprolactinaemia is gel-filtration chromatography, which is expensive and time-consuming, so polyethylene glycol (PEG) serum precipitation is used as a screening method. The diagnosis of macroprolactinaemia is made when a PEG precipitation ratio is greater than 60% or recovery of less than 40% after PEG [91].

Macroprolactin is not considered to have significant biological activity, but it retains partial or total immunoreactivity with anti-PRL antibodies used in commercial immunoassays. Detection of macroprolactin is clinically important to avoid incorrect diagnosis and unnecessary investigations.

Nevertheless, later investigations revealed that some patients with macroprolactinaemia could have symptoms of hyperprolactinaemia or abnormal findings of the anterior pituitary, but in far lesser degree compared with patients with true hyperprolactinaemia [93]. Therefore, the presence of menstrual disorders, galactorrhoea ,and/or infertility in hyperprolactinaemic patients does not exclude macroprolactinaemia. Galactorrhoea was found in 46%, menstrual disorders in 39%, infertility associated with galactorrhoea or with menstrual irregularities in 28% of macroprolactiaemic patients [85].

Some authors recommend that the screening for macroprolactiaemia should be done in all hyperprolactinaemic patients [90, 93], the others consider that it is mostly indicated for asymptomatic patients, in apparent idiopathic hyperprolactinaemia and any patients without an obvious cause for the hyperprolactinaemia [46].

Idiopathic Hyperprolactinaemia

Idiopathic hyperprolactinaemia is defined as hyperprolactinaemia of unknown etiology, ie when its secondary causes have been ruled out and pituitary nuclear magnetic resonance (NMR) is normal [77, 94, 95]. The prevalence of idiopathic hyperpolactinaemia varies from 3.6% among patients with hyperpolactinaemia, to as much as 87.97% in hyperprolactinaemic infertile women [88].

Possible explanations for idiopathic hyperprolactinaemia include: immunological causes (formation of antipituitary antibodies) [96], the existence of very small microprolactinomas that could not be detected with current imaging techniques [78], or differences in prolactin receptor function (novel hypothesis) [97].

Treatment of Hyperprolactinaemia in Women

Indications for lowering high serum PRL levels are: anovulation and subsequent infertility, treatment of galactorrhoea that represent a problem to the patient, and treatment of the manifestation of the hypoestrogenic state to prevent osteoporosis and improve the quality of life.

Treatment options for hyperprolactinaemia are listed in Table 3.

Table 3 Treatment options for hyperprolactinaemia in clinical practice

Dopamine agonist
▪ ergot derivates: bromocriptine, cabergoline, pergolide, lisuride etc.
▪ nonergot derivate: quinagolide
Surgical treatment for prolactinomas

Dopamine agonists are the first line for the medical treatment of hyperprolactinaemia in women with anovulation as sole reason for infertility, being successful in restoring ovulation in up to 80% of infertile patients with hyperprolactinaemia.

Bromocriptine is safe for the treatment of the patients with hyperprolactinaemic anovulation and infertility, due to its safety in early pregnancy. Bromocriptine has been used for almost 50 years with no reported fetal harmful effects. The long term follow-up of the children born by mothers taking bromocriptine in early pregnancy showed the absence of any adverse effects [98].

In our practice, we start bromocriptine with a dose of 1.25 mg/day, or even less, before sleeping due to side effects. It can be titrated to a maximum of 7.5 mg/day for the treatment of hyperprolacatinaemic anovulation and infertility. The half-life of bromocriptine is about 6 hours, so we consider that daily dose should be divided into two or three smaller doses, which offer better control of circadian variations of prolactin serum levels, as well as better control of nocturnal prolactin levels. Side effects of bromocriptine included nausea, dizziness, headache, and postural hypotension, as common side effects of dopamine agonists .

The unusual side effects of the bromocriptine therapy are hallucinations due to similarity of the bromocriptine molecule to LSD (in 1-2%). We have seen such effects in our patients: one had scintillations and another had seen a fire on the electric stow. The more often problem is possibility of low concentration during the bromocriptine therapy and the patient should be warned on such effect.

Cabergoline is also an effective dopamine agonist. It was reported that cabergoline is better tolerated and more successful in achieving pregnancy than bromocriptine [99, 100].

The half-life of the cabergoline is 65 hours, so it is administered once (0.8 mg) or twice (0.4 mg) a week, with a maximal dose of 1–2 mg/week. The incipient dose of cabergoline could be as small as 0.25 mg twice a week, with a gradually increase to 0.5 mg twice a week according to the effects of therapy. It is more comfortable for the patient than bromocriptine. Cabergoline is safe during early pregnancy according to fetal anomalies [101-103], but the studies of other possible effects on fetal development are still missing. The problem with cabergoline is also a development of cardiac valvular disease due to possible thickened of cardiac valves caused by cabergoline effects on mitogenesis and fibroblast proliferation, which has been seen in patients with Parkinson's disease taking higher doses of cabergoline (4 mg/day – much higher than the dose for hyperprolactinaemia) [104, 105].

Nevertheless, the development of constrictive pericarditis during cabergoline therapy for hyperprolactinaemia (and smaller doses) has been also reported, so echocardiography in 6 to 12 months intervals is mandatory for patients receiving cabergoline [106].

Quinagolide, a nonergot dopamine agonist, is also successful in the treatment of infertile patients with hyperprolactinaemia [107].

Quinagolide has a higher affinity to D2 receptors and a longer half-life (22 hours) than bromocriptine, so it is administered once a day [108]. The initial dose is 25 – 50 micrograms once a day; with a gradual increase to 75 micrograms once a day.

Quinagolide is well tolerated and safe in early pregnancy [109].

In patients with prolactinomas, dopamin agonists are successful in achieving normal PRL serum levels in 71% and tumour shrinkage in 80% of all cases [110]. In the case of the rising prolactinoma, it was recommended to use cabergoline in preference to other dopamine agonists because it has a higher efficacy in normalizing PRL levels, as well as better results in pituitary tumour shtrinkage. Cabergoline greater efficacy may be explained by its higher affinity for dopamine receptor binding sites [38].

Surgical treatment (nasosphenoidal approach) is reserved for growing macroprolactinomas or those associated with neural manifestations. Microprolactinomas do not need such interventions. Moreover, it was recommended that asymptomatic microprolactinomas should not be treated with dopamine agonists. It was suggested that patients with amenorrhoea and microadenoma should be treated with dopamine agonists or oral contrarceptives [38]. The growth of the tumour during the therapy with oral contraceptives is extremely rare, but the patient should be warned on the symptoms and possibility of the rise of the intracranial pressure [68, 69, 74].

Conclusion

Hyperoprlactinaemia is one of the most frequent causes of anovulation, resulting in infertility and hypoestrogenic state with consequences on overall women's health. There are numerous etiological factors of hyperprolactinaemia, therefore, taking proper medical history and clinical assessment are crucial for correct differential diagnosis and proper therapy. Macroprolactinaemia and "hook

effect" must be considered in the evaluation of hyperprolactinaemia. Indications for the treatment of hyperprolactinaemic female patient are infertility, galactorrhoea that represents the problem for the patient, and hypoestrogenic state. Dopamine agonists are successful in lowering PRL serum levels and restoring ovulation and represent the main option for the treatment of the female patient with hyperprolactinaemia.

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