

A SCOPING REVIEW OF HYPERPROLACTINEMIA AND RECENT TRENDS IN ITS THERAPEUTICS

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Abstract

Hyperprolactinaemia is a prevalent disorder of the hypothalamus-pituitary axis, predominantly affecting females. Etiological causes of hyperprolactinemia vary from being physiological, drug-induced, or secondary to a pathological condition. The most frequent aetiologies of pathological hyperprolactinemia are drugs and sellar/parasellar masses, particularly those that secrete prolactin or act through the "stalk effect." Common manifestation includes hypogonadism and galactorrhoea. However, recent research has revealed that its impact on bone health, metabolism, and the immune system is also becoming more extensive. The diagnostic approach requires identification of the underlying cause, which necessitates detailed history taking and clinical evaluation. When interpreting the biochemical reports on prolactin, it is important to consider preanalytical and analytical issues such as the presence of macroprolactin or the hook effect. The primary objective of treatment is to reinstate and uphold typical gonadal function and fertility while also averting osteoporosis. Other management approaches are contingent upon the root cause of the condition. Dopamine agonists are the preferred treatment option, whereas surgery and radiotherapy are considered in DA resistance cases. This review aims to provide healthcare professionals with a comprehensive overview of hyperprolactinemia, focussing on the diagnostic and management strategies employed for patients with hyperprolactinemia.

INTRODUCTION

The hypothalamic-pituitary axis maintains physiological homeostasis through a complex interaction between feedback mechanisms and neuroendocrine pathways. Hence, any defect in this axis is bound to have long-term alterations resulting in neuroendocrine and metabolic disruption. Hyperprolactinemia is a prevalent endocrine disorder of the hypothalamic-pituitary axis most commonly observed in females, with its prevalence varying from 0.5 to 17%. Specifically, a prevalence of 5% has been documented in infertility clinics, 9% in women experiencing adult-onset amenorrhea, and 17% in women diagnosed with polycystic ovary syndrome.^[1] Pathological hyperprolactinemia refers to a condition with consistently high levels of plasma prolactin (PRL) after excluding any physiological causes of PRL hypersecretion. The polypeptide hormone PRL

shares a common tertiary structure with other growth hormones and placental lactogen hormones as they are evolutionarily related. However, in the early 1970s, PRL was identified as a distinct entity primarily due to the development and advancement of radioimmunoassay. This breakthrough allowed for deeper insights into the hormone and its related pathophysiological conditions.^[2] PRL is secreted by the anterior pituitary glands. But unlike other tropic hormones, prolactin secretion is chiefly regulated by hypothalamic inhibition and is not regulated by negative feedback from peripheral hormones, either directly or indirectly. It is self-regulated by auto-inhibition through the hypophyseal pituitary portal system that triggers hypothalamic dopamine release, thereby inhibiting the pulsatile secretion of gonadotropin-releasing hormone (GnRH). This inversely modulates the release of gonadal-regulating hormones from the pituitary. The translated mature

product of the gene is a 23KDA, 199-amino-acid single-chain polypeptide with three intramolecular disulfide links. At the tertiary level, PRL consists of four main anti-parallel α helices, a structural similarity with many other cytokines.^[3,4] Variants of PRL are known to exist due to post-translational modifications. The immunologically active Big PRL (B-PRL) and Big, Big PRL (BB-PRL) have molecular weights of 48000 to 56000 Daltons and 100,000 Daltons, respectively. These larger PRL molecules may be bound by immunoglobulin G or be dimers or tetramers of the natural hormone. However, they exhibit lower biological activity compared to the small PRL monomer.^[5,6] Studies have reported 40% homology between PRL and GH gene located on chromosome 17.^[7,8]

The lactotroph cells in the adenohypophysis region of the pituitary gland secrete the majority of prolactin. Recent studies have shown that extra pituitary sites such as lymphocytes, lactating mammary glands, placental cells, and epithelial breast cancer cells also release prolactin where they exert their physiological action either locally, by autocrine or paracrine action or in an endocrine manner. However, PRL gene expression differs in the pituitary, where it is driven by Pit-1, which is responsible for higher expression compared to extra pituitary organs such as T-cells and the uterus; an upstream promoter regulates it. Prolactin exerts its physiological effect by binding to the cytokine receptor superfamily member prolactin receptor (PRL-R), a transmembrane protein that is predominantly found in breast and ovarian tissue but also expressed in other peripheral tissues.^[9-12] As mentioned, hyperprolactinemia is one of the most common pituitary hormone abnormalities with broad aetiology; idiopathic, physiological, and pathological. Moreover, the clinical presentation may also vary from being severely affected to being completely asymptomatic. In view of this, this review intends to summarize and refresh the current knowledge regarding prolactin, and its effect on various tissues, as well as outline the recent trends in managing patients with hyperprolactinemia.

Data Collection

For this scoping review, PubMed, Scopus, and Google Scholar were searched and screened using different combinations of keywords, prolactin, prolactinomas, and hyperprolactinemia until March 31, 2023. The titles and abstracts of the articles were screened, and relevant articles were selected. Both review articles and original articles written in English were included, and articles whose full text could not be accessed were excluded. EndNote X6 was used for citing the article.

RESULTS

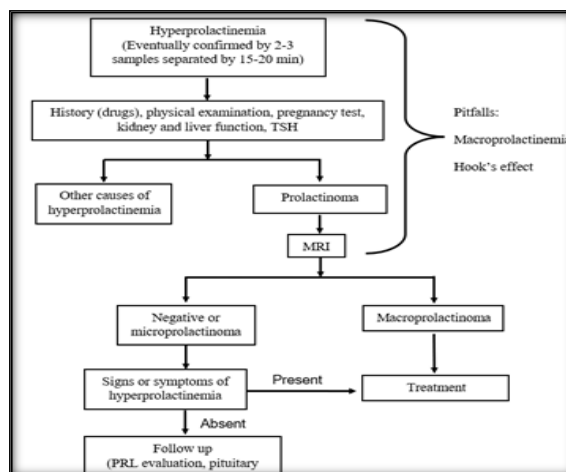


Figure 1: A flowchart depicting the diagnostic approach to hyperprolactinemia

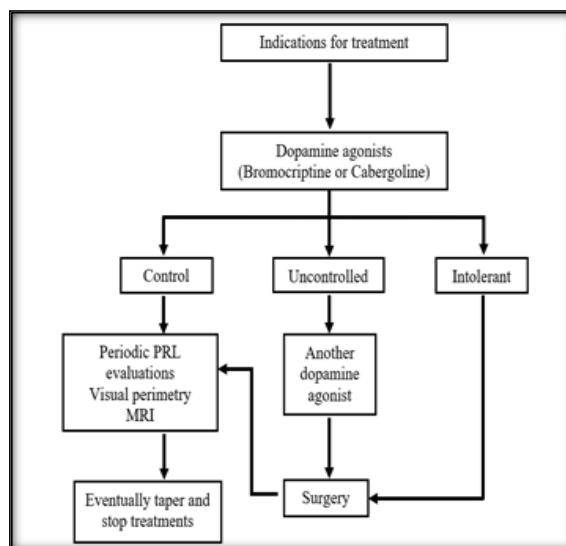


Figure 2: A flowchart showing the treatment approach in case of hyperprolactinemia

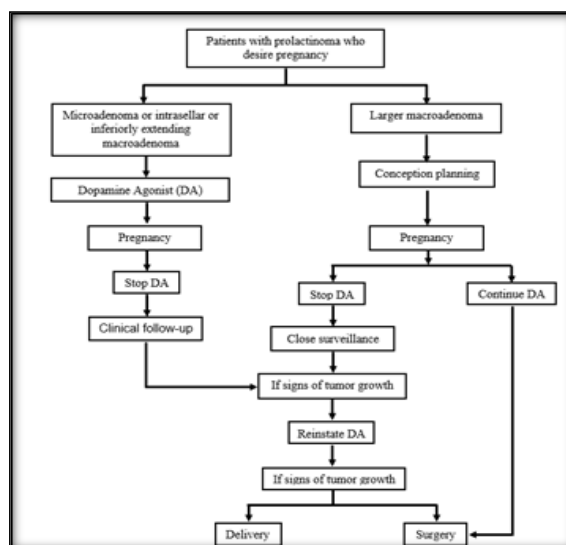


Figure 3: A flowchart showing the treatment protocol for hyperprolactinemia in pregnancy

Table 1: Causes of hyperprolactinemia

Physiological	Pharmacologic	Pathologic
Stress	Neuroleptics	Prolactinoma
Sleep	SSRIs	Non-functioning pituitary tumors
Lunch/ dinner	H2-receptor blockers	Empty sella syndrome
Chest wall stimulation	Methyldopa	Infiltrative disorders or CNS masses
Pregnancy	Verapamil	Hypothyroidism
	Reserpine	Kidney failure
	Metoclopramide	Idiopathic
	Protease inhibitors	

Table 2: Clinical manifestation of hyperprolactinemia in males and females. The manifestation is due may be due to hypogonadism secondary to hyperprolactinemia or the mass effect of macroadenoma

In Females	In Males
Subfertility	Subfertility
Oligomenorrhea	Decreased potency
Amenorrhea	Decreased libido
Osteopenia	Reduced muscle mass
Galactorrhea	Loss of pubic hair
Hirsutism	Galactorrhea
Decreased libido	Gynecomastia
Acne	Osteopenia
Mass Effect (usually macroadenoma)	
Headache	
Loss of vision	
Hypopituitarism	
Cranial neuropathies	
CSF rhinorrhea	
Seizures	

DISCUSSION

3.1 Pituitary PRL secretion and control

Prolactin is released in a pulsatile manner, with peak levels occurring during non-rapid eye movement (NREM) sleep while exhibiting circadian variation throughout the day.^[13,14] The secretion of pituitary PRL is well-regulated. Dopamine, the major inhibitor, is released by the hypothalamus via the neurons of arcuate and the paraventricular nuclei present in the medial basal hypothalamus, which reaches the pituitary via the hypothalamus-hypophyseal portal circulation. Thyrotrophin-releasing hormone (TRH), vasopressin, oxytocin, and vasoactive intestinal polypeptide are all neuropeptides stimulating PRL release. Besides this, there is also autoregulation by PRL itself through a short feedback loop, as elevated levels of prolactin have been observed to increase dopamine synthesis in the hypothalamus and its concentration in the portal blood.

3.2 Physiological action of PRL

Prolactin is released in a pulsatile manner, with peak levels occurring during non-rapid eye movement (NREM) sleep, while exhibiting circadian variation throughout the day.^[13,14] The secretion of pituitary PRL is well-regulated. Dopamine, the major inhibitor, is released by the hypothalamus via the neurons of arcuate and the paraventricular nuclei present in the medial basal hypothalamus, which reaches the pituitary via the hypothalamus-hypophyseal portal circulation. Thyrotrophin-releasing hormone (TRH), vasopressin, oxytocin, and vasoactive intestinal polypeptide are all neuropeptides stimulating PRL release. Besides this, there is also autoregulation by PRL itself through a

short feedback loop, as elevated levels of prolactin have been observed to increase dopamine synthesis in the hypothalamus and its concentration in the portal blood. Prolactin elicits three primary biological responses in humans, namely steroidogenesis, lactogenesis, and immune regulation. During pregnancy, a hyper-estrogen state result in lactotroph proliferation and enhanced PRL production. In the breast, PRL stimulates the production of milk proteins, i.e., casein, lactalbumin, and lactoglobulin, once there is a post-partum reduction of estrogen. The precise function of PRL in normal ovaries is not yet fully established. However, Mc Natty et al., and other research have shown that PRL is required for progesterone synthesis by the human granulosa cell at low physiological quantities. Conversely, high concentrations of PRL have been found to be inhibitory in vitro.^[15,16] Human studies have shown that when plasma PRL levels exceed 100 ng/ml, antral fluid PRL levels rise while follicle-stimulating hormone (FSH) levels fall, thereby counteracting the stimulating effects of FSH on aromatase activity. This reduces estrogen production.^[17]

The precise physiological function of PRL in adrenal steroidogenesis remains unclear. However, most studies show that 50% of women with hyperprolactinemia had moderately increased plasma dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS).^[17] The presence of PRL-R on the T-Cells and B-Cells indicates that prolactin maintains immunocompetency, however, it is still being studied. The remission of active systemic lupus erythematosus (SLE) in bromocriptine-treated patients supports other human and experimental investigations linking hyperprolactinemia to SLE activity.^[4,18] Although few animal studies have

confirmed the potential of locally released prolactin to induce tumorigenesis, such data have been lacking in humans though there is evidence of local synthesis in prolactin in breast and prostate tissue.^[19,20] Hayder et al. found that elevated plasma PRL levels may exacerbate the severity of Covid-19 by activating immune cell cytotoxicity, producing pro-inflammatory cytokines, suppressing Treg cells, and inducing B cell auto-reactivity. High PRL serum levels in Covid-19 are unclear. Though the exact mechanism of this exacerbation is still poorly understood, reactive oxidative species damage, stress, and dysregulation of the immune process could play an important role. In addition, it is plausible to suggest that Covid-19-induced hyperprolactinemia may be attributed to high levels of pro-inflammatory cytokines, as well as elevated levels of TRH, Angiotensin II (Ang II), and vasopressin (AVP).^[21]

3.3 Causes of hyperprolactinemia

The diagnosis of hyperprolactinemia is established when the concentration of serum prolactin levels exceeds the normal reference range (usually 400–500 μL or 20–25 ng/ml) on two separate occasions.^[22] Causes of hyperprolactinemia may be physiological, pharmacological, or pathological, which are summarized in Table 1. Common causes include pregnancy, hypothyroidism, dopamine antagonist drug therapy (including phenothiazines and metoclopramide), and sometimes the short-term stress of venepuncture. Hyperprolactinemia is common among patients with symptoms of hyperprolactinemia, but more than 50% of cases are due to pharmacological treatments or improper sample extraction.^[23] Hyperprolactinemia is a feature of polycystic ovarian syndrome in a proportion of cases. Of the pituitary causes, prolactin-secreting microadenomas and idiopathic hyperprolactinemia are the most common. Pituitary adenomas occasionally co-secrete PRL and other anterior pituitary hormones, which results in elevated PRL levels. Clinically significant pituitary adenomas have a mean prevalence of 89.1 per 100,000 (range, 75.7–115.6 per 100,000), with a majority (close to 70%) being female.^[24] Pituitary stalk disruption by a variety of local pathologies, such as non-functioning adenomas, craniopharyngiomas, and gliomas, can lead to hyperprolactinemia by interfering with the normal suppression of prolactin by hypothalamic dopamine. About 50% of newly diagnosed pituitary adenomas every year are prolactinomas, which are the most prevalent cause of tumoral hyperprolactinemia, which exhibits a prevalence of 100 per one million population. Most prolactinomas are microadenomas, which are less than 10 millimeters in size and cause hyperprolactinemia-related symptoms. However, macroadenomas, which are larger than 10 millimeters in size, can cause mass effects. Prolactinomas are typically detected in the female population during the second to fourth decade of life. However, after 50 years of age, the incidence is similar in males and females.^[25,26]

3.4 Clinical features of hyperprolactinemia

The clinical manifestations of a patient with prolactinoma are summarized in Table 2. Persistent hyperprolactinemia directly disrupts gonadal sex steroid production by interfering with the pulsatile secretion of gonadotropin-releasing hormone, which in turn limits the release of luteinizing hormone and follicle-stimulating hormone.^[27,28] Hence, the overall effect causes clinical manifestations in both males and females. Females present earlier with the typical amenorrhea-galactorrhea syndrome, while males usually appear late with signs of compression rather than decreased libido, gynecomastia, and impotency, which they disregard. Kulshreshtha et al., in their study, reported that the prevalence of galactorrhea in hyperprolactinemic women ranged from 35% to 65%, with 20% of women with secondary amenorrhea and 75% of women with both amenorrhea and galactorrhea having hyperprolactinemia.^[29] The clinical presentation varies depending on the degree of increase in PRL. In females with mild elevation (31–50 ng/mL), a shorter luteal phase, infertility, and decreased libido are seen. Those with a moderate elevation (51–75 ng/mL) present with oligomenorrhoea, whereas a marked increase above 100 ng/mL presents with hypogonadism, amenorrhea, and galactorrhea. In men, galactorrhea is rare and usually associated with high PRL levels. Gynecomastia may occur in men, but it is usually a consequence of secondary hypogonadism rather than a raised PRL level. Other clinical manifestations in postmenopausal women include osteopenia and osteoporosis, secondary to hypoestrogenism, resulting from elevated PRL levels. Less frequent manifestations of hyperprolactinemia include the development of hypopituitarism, osteoporosis or osteopenia, and alopecia.^[30]

There is some clinical evidence that patients with hyperprolactinemia are prone to weight gain, which resolves when dopamine agonists suppress the PRL levels and may relate to the emerging effects of PRL on adipose tissues.^[31] Studies have shown that hyperprolactinemia may be linked to mild psychological manifestations, including anxiety, depression, and hostility, which may persist despite successful reduction of prolactin levels.^[32,33]

3.5 Evaluation of hyperprolactinemia

A thorough past, medical, drug, and family history, along with a detailed physical examination of a patient with hyperprolactinemia, focusing on any signs and symptoms of PRL, should be obtained, as indicated in Figure 1. Upon confirmation, the initial diagnostic goal should be to identify a likely non-tumor cause in order to minimize the hazards and costs of unneeded CT and MRI scans. If the PRL levels are not diagnostic, the levels should be reassessed on a different day, at least an hour after the patient has woken up or eaten. The immunoassay can be impacted by pre-analytical error; hence, certain prerequisites must be followed. Two to three blood samples should be taken at intervals of 15 to 20

minutes to minimize the effect of pulsatile secretion.^[34] Drugs known to elevate PRL levels should be withdrawn, usually for 48 to 72 hours, with appropriate advice from a specialist physician, such as a psychiatrist or cardiologist. In drug-induced hyperprolactinemia, PRL levels rarely exceed 150 µg/L.^[32,34] Renal, liver, and thyroid function should be tested. A pregnancy test to rule out pregnancy-related hyperprolactinemia should also be performed. The "hook effect" and macroprolactinomas are two potential pitfalls that contribute to the analytical errors of PRL. Macroprolactin is a compound consisting of prolactin and typically an immunoglobulin G (IgG) antibody.^[35] Macroprolactinemia levels should be measured via polyethylene glycol (PEG) precipitation and excluded in an asymptomatic or atypical presentation. Gel filtration chromatography is another method that is time-consuming, expensive, and not used in clinical laboratories. The hook effect, generated by an exceptionally high PRL level, can cause deceptively low PRL levels due to its interference with the assay. Repeating the experiment after a 1:100 serum sample dilution can confirm this. All patients with significant pituitary adenomas and PRL levels below 200 ng/mL should consider the hook effect and have a repeat assay performed with dilution.^[36]

Prolactinomas are diagnosed by gadolinium-enhanced MRI after all other possible secondary causes of hyperprolactinemia have been ruled out. MRI is preferred over CT as CT may miss small lesions while exposing patients to large doses of radiation. It is worth noting that a normal MRI does not rule out a microadenoma, and 10% of the normal population has incidentalomas, which are microadenomas. Hence, some studies recommend MRI for PRL levels above 100 ng/ml. Some advocate it for all individuals with consistently increased PRL levels without a secondary cause of hyperprolactinemia.^[37]

The presence of a macroadenoma with serum PRL levels above 250 ng/mL is always associated with macroprolactinomas. However, its association with mild hyperprolactinemia most likely confirms a non-PRL-producing pituitary adenoma or craniopharyngioma causing the "salt effect". Once macroadenoma is confirmed, the patient should be further screened for hypopituitarism through evaluation of the levels of other anterior pituitary and end-organ hormones (ACTH, LH, FSH, GH, TSH, free TH, glucose tolerance test, cortisol, testosterone, estradiol, and insulin-like growth factor-1).³⁸ Some clinicians perform an initial basal hormone assessment to rule out subsequent hypothyroidism and hypoadrenalism from severe pituitary illness and excess GH release from mammosomatotrophic pituitary tumors. Goldman perimetry should be performed on macroadenoma patients with sella extension. Idiopathic hyperprolactinemia occurs when other reasons have been ruled out and an MRI shows no adenoma.^[38]

3.6 Treatment of hyperprolactinemia

As with most tumors, pituitary adenomas may be treated using medical, surgical, or radiotherapy approaches. The main objectives of therapy are twofold: firstly, to decrease the size of the tumor, and secondly, to achieve normalization of prolactin levels while fully restoring gonadal and sexual function, including fertility. Nevertheless, with regard to prolactinoma, the efficacy of medical treatment has reached a level where alternative modalities are seldom employed.

3.6.1 Indications for treatment

All cases of macroadenomas must be treated. In the case of microadenoma and mild galactorrhoea, the current guidelines suggest no medical intervention but reassure postmenopausal and premenopausal women with regular cycles, while treatment is advocated for those presenting with troublesome galactorrhoea, infertility, persistent hypogonadism, delayed sexual maturation, and bone loss.^[39] However, in mild cases, regular follow-up with periodic determination of PRL levels should be done. If the PRL rises or symptoms of a mass effect develop, an MRI should be performed. Prolactinomas are frequently remarkably dormant over many years, with little or no progression, even when left untreated, and occasionally resolve spontaneously.^[39]

3.6.2 Drug Therapy

Dopamine agonists (DA) are known to have a substantial impact on the management of hyperprolactinemia, both in cases of idiopathic/non-tumoral and prolactinoma-related PRL excess and are considered the gold standard for the treatment of microprolactinomas and macroprolactinomas. DA inhibits the synthesis and release of PRL by acting on dopamine D-2 receptors in pituitary lactotroph cells.⁴⁰ Long-term administrations of DA can be cytotoxic to the tumor. Prolactinomas resistant to DA may need surgical removal via a transsphenoidal approach (Figure 2).^[41]

The most widely prescribed DAs are cabergoline and bromocriptine. Nonergot (quinagolide, lisuride, and terguride) and ergot (pergolide) DA make up the rest of the class. Dopamine agonists have succeeded remarkably in achieving PRL suppression and tumor shrinkage in 80–90% of patients. Even in patients with large macroadenomas, tumor shrinkage by at least 25% of volume can be seen in approximately 80% of patients on cabergoline. Restoration of ovarian function occurs in almost 90% of women, although in male patients, the testicular function is less completely restored, and up to 50% may require testosterone replacement therapy despite apparently adequate suppression of PRL levels. The remission rates of cabergoline and primary surgical resection of microprolactinomas and enclosed macroprolactinomas, when conducted by proficient pituitary neurosurgeons, are comparable.^[42-44]

The first dopamine agonist drug to be marketed was bromocriptine, which is still frequently used today. It is often given two or three times a day with food to avoid the common side effect of nausea. Other

common side effects include postural hypotension, dizziness, headaches, and constipation. Psychosis is a rare complication, but milder depressive symptoms may be quite common. Because of the frequency of these side effects, other dopaminergic agonists have been developed with better selectivity for D-2 receptors, and cabergoline and quinagolide are now widely used with similar efficiency in both PRL suppression and tumor shrinkage to bromocriptine.⁴⁵ Cabergoline has the highest affinity and greatest selectivity for D-2 receptors and is usually given once or twice a week, while quinagolide is administered once daily. Both drugs are associated with fewer adverse reactions than bromocriptine, and both are now more commonly used as a first choice in most patients. However, all three drugs are still recommended to start treatment with low doses and gradually build up to the recommended dose to avoid nausea and postural dizziness. In general, patients are maintained on the minimum effective dose that will allow restoration of ovarian function and suppression of galactorrhea. In their research, Chen et al. suggested that cabergoline be used as a first-line treatment for hyperprolactinemia due to its efficacy. Transsphenoidal surgery has been demonstrated to be effective in some studies, even when compared to medicinal treatment. Surgical intervention may re-emerge as an alternative primary treatment option. Surgery offers a higher rate of disease remission when combined with cabergoline than either drug or operation alone.^{46]}

Females starting treatment with DAs should be warned to expect the restoration of ovulatory menstrual cycles, generally within weeks. It is recommended that females who do not desire pregnancy be counselled to use contraception since it may not be readily evident that their fertility has been re-established (refer to figure 3).

3.6.3 Resistance to DAs

As per the guidelines set forth by the Endocrine Society, DA resistance is characterized by the inability to attain normal prolactin levels and achieve a 50% reduction in tumor despite being administered maximally tolerated doses.^[35] Resistance to DAs in prolactinomas is due to the low density of membrane D-2 receptors in certain lactotroph tumors. It has been reported that patients with DA resistance may show a reduction in serum PRL levels with no reduction in tumor size, whereas some experience changes in tumor size without any effect on prolactin levels. Increasing the DA dosage gradually, switching DAs, and ultimately resorting to transsphenoidal pituitary surgery are the current methods used to treat DA resistance. DA-resistant prolactinomas may benefit in the future from PRL-R antagonists, which are similar to GH-receptor antagonists used in acromegaly. However, those who are resistant to or unable to take DA should still consider surgery.^[47]

3.6.4 Surgical treatment and radiotherapy

With a good success rate in controlling hyperprolactinemia and the major advantage of avoiding the risk of pituitary insufficiency with a

medical approach, the indication for surgical resection of prolactinomas is limited. Although surgery can provide a long-term cure, remission rates are just about 60%.^[48] Surgical intervention is reserved for cases with DA resistance or persistent tumor mass effects despite maximal DA treatment, patients with a low tolerance for therapy, or those who are reliant on antipsychotic treatment. Curative surgery with neurosurgical skills may be an alternative for young individuals with microprolactinomas who want to forgo long-term pharmacological therapy.^[48,49]

Radiotherapy is rarely used because of the high risk of adverse effects such as damage to the optic nerve, anterior hypopituitarism, and cerebrovascular diseases associated with external beam radiation to the hypothalamus-pituitary region. It can be helpful for macroprolactinoma patients who haven't responded to other treatments or for whom medical or surgical options have shown no improvement.^[50]

3.6.5 Miscellaneous Issues in Treatment

3.6.5.1 Use of oral contraceptives (estrogens)

Despite their success, DAs have significant side effects, and up to 10% of patients also have to discontinue the treatment. In hyperprolactinaemic females who are intolerant to DAs or intend not to get pregnant, estrogen replacement therapy may be initiated to mitigate the risk of osteoporosis or to enhance sexual drive. In cases where galactorrhea is not a significant concern, hypogonadal women with microprolactinomas may receive treatment for their hypogonadism through the use of combined oral contraceptive agents with regular monitoring of PRL levels.^[39,51,52]

3.6.5.2 Menopause

Hyperprolactinemic postmenopausal females rarely present with galactorrhea as they have low estradiol levels due to cessation of ovarian function. They are clinically diagnosed when they present with symptoms of mass effect, such as headaches and impaired vision, as a result of an increase in the size of the adenoma.^[53] The diagnosis of prolactinoma in postmenopausal women is delayed as the typical symptoms of PRL excess, such as infertility and oligomenorrhoea, are not present in these females. This presents a challenge for clinicians to identify and delay the diagnosis. If galactorrhea is not a problem, and there is no significant pituitary mass lesion, then the protection of ovarian function is no longer an issue, and therapeutic treatment is not necessary, as reassurance would suffice.^[54] Estrogen replacement can be used in these women if they wish for symptom control or are concerned about bone mineral density, provided PRL level and pituitary anatomy are monitored.

3.6.5.3 Antipsychotic medication

Hyperprolactinemia induced by psychoactive drugs presents a dilemma for the clinician, as DA therapy could exacerbate the risk of psychosis.^[55] In this case, the management options are limited to the exclusion of structural or anatomical abnormalities in the hypothalamus-pituitary axis. Hence, based on the

psychiatric manifestation, the management may be monitored and modified; for instance, olanzapine may be substituted as it has a milder effect on PRL secretion.

3.6.5.4 Pregnancy and hyperprolactinemic females

Approximately 90% of women with anovulation secondary to hyperprolactinemia respond well to DA therapy and start ovulating. As per the guidelines of the European Society, DA should be withdrawn as soon as a female with prolactinoma gets pregnant to avoid any teratogenicity during pregnancy and lactation. Upon the termination of DA therapy, the fetus may be exposed for up to four weeks of gestation. However, no adverse effect on the growing fetus has been reported. If a patient with macroadenomas on treatment with DA, with no prior history of surgical intervention or radiotherapy, conceives, DA may be continued throughout the pregnancy, specifically if the tumor infiltrates the optic chiasma (Figure 3).³ While the safety of bromocriptine during pregnancy has been established, data on cabergoline and quinagolide remain limited. Because DAs inhibit lactation, they should be avoided during the postpartum period if the patient wishes to breastfeed.^[39]

The hyperestrogenic state of pregnancy stimulates the pituitary to enlarge up to three times. Around 35% of pregnant women experienced a PRL reduction or normalization in their postpartum phase, compared to 14% of non-pregnant women. A reduction in PRL levels or normalization subsequent to pregnancy has been observed in 35% of instances, in contrast to 14% in nulliparous individuals. The curative effect of pregnancy on prolactinoma may be attributed to the necrosis or microinfarction of the adenoma caused by estrogens. This warrants follow-up of serum PRL levels for several months post-pregnancy before considering medical treatment.^[56,57] Pregnancy is associated with a risk of tumor enlargement in 1.3% of patients with microprolactinoma and over 30% in patients with macroprolactinoma. The collective risk decreased to 5% when macroprolactinomas were surgically treated or irradiated prior to pregnancy. Hence, in cases of macroadenomas, it is recommended to plan conception only after significant tumor shrinkage to minimize the risk of optic chiasma compression during pregnancy. DAs may be reconsidered in cases where the tumor increases in size. However, if the tumor continues to enlarge, the recommended option is delivery, provided it has reached the state of viability, or transsphenoidal surgery.²⁵ It is recommended that women receive counseling regarding the potential risks associated with pregnancy prior to conception. Additionally, it is advised that they receive guidance on the importance of close clinical monitoring throughout their pregnancy. Routine monitoring of PRL levels during pregnancy is not recommended as they are not reliable indicators of tumor growth. Neuroimaging and visual field assessment are indicated for women with microprolactinomas only if

there are symptoms that indicate tumor enlargement. It is recommended that women with macroadenoma undergo monthly visual field testing and repeat scanning should only be conducted if there are indications of tumor enlargement or symptoms.^[56,57]

3.6.5 Remission of hyperprolactinemia and prolactinoma

According to a recent study, it has been advocated that prolactinoma patients may not need continuous DA therapy. The DAs may be reduced or stopped within two to five years, particularly in patients with negative pituitary MRI studies during treatment. Extended follow-up is necessary, along with careful observation for the relapse of hyperprolactinemia and the resurgence of tumor growth. Patients with macroprolactinomas and microprolactinomas who had small remnant tumors visible on MRI scans at the time of cessation of treatment had a higher estimated rate of recurrence at five years compared to patients whose scans showed no evidence of tumor at the time of withdrawal.^[25]

CONCLUSION

Pathological increase in prolactin is associated with hyperprolactinemia, the most common disorder of the hypothalamus-pituitary axis. The detection of hyperprolactinemia serves as the initial step in a comprehensive diagnostic approach, rather than the final conclusion. It is imperative to identify the root cause of the disorder before commencing any treatment. Indications of hypogonadism or mass effect of a prolactin-secreting tumor require immediate treatment. In the majority of cases, DA is the preferred choice of treatment. However, in cases where patients do not respond well or cannot tolerate medical therapy, surgery may be considered as an alternative option. Bromocriptine is currently the preferred DA for females requiring medical intervention for infertility. In comparison, Cabergoline has superior tolerability and a longer half-life. However, their effectiveness and safety in the management of infertility though promising, are still a matter for investigation and require large-scale studies. Postmenopausal and asymptomatic premenopausal women with microadenoma and mild galactorrhoea should be reassured and followed up with regular prolactin estimation. However, the determination of prolactin concentration can be influenced by a variety of factors, including both pre-analytical and analytical errors, which severely affect the accuracy and reliability of the result obtained. Preanalytical errors can occur due to factors such as the pulsatile release of hormones, interference of drugs, and stress. On the other hand, analytical errors can arise from Hook's effect and macroprolactinoma. Hence it is crucial that the clinicians and laboratory physicians collaborate closely to ensure that the results obtained are reliable and can be used to make informed decisions regarding patient care and provide the best care possible.

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