Updated Clinical Features and Diagnostic-Therapeutic Essentials of Pituitary Prolactinomas: An Interpretation of the 2022 ICCE/AME Clinical Practice Consensus

Authors: Tan Huiwen, Li Danting, Yu Yerong, Yu Yurong

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Abstract

Pituitary prolactinoma is a neuroendocrine disorder caused by excessive synthesis and secretion of prolactin from pituitary lactotroph adenomas. Standardized diagnosis and treatment of pituitary prolactinoma is of great significance for restoring and maintaining normal pituitary function and improving patients' quality of life. In January 2022, the European Journal of Endocrinology published the latest clinical practice consensus statement on pituitary prolactinoma by the International Committee of Clinical Endocrinology (ICCE) and the Italian Association of Clinical Endocrinologists (AME)—the "2022 ICCE/AME Clinical Practice Consensus on Pituitary Prolactinoma" (hereinafter referred to as the "2022 ICCE/AME New Consensus"). Based on the latest evidence-based medical evidence, the 2022 ICCE/AME New Consensus provides systematic exposition, analysis, and recommendations on clinical diagnosis and treatment issues of pituitary prolactinoma. This article offers an interpretation focusing on the updated key points regarding diagnosis, treatment, special populations, dopamine agonist resistance, and invasive disease of pituitary prolactinoma in the 2022 ICCE/AME New Consensus, hoping to contribute to the understanding of pituitary prolactinoma among general practitioners and endocrinology specialists, and to provide a reference for standardized diagnosis and treatment in their clinical practice.

Full Text

Interpretation of the 2022 ICCE/AME Position Statement for Clinical Practice in Pituitary Prolactinoma: Update on Clinical Characteristics and Key Points in Diagnosis and Treatment

TAN Huiwen[12], LI Danting[1], YU Yerong[12]*

[1]Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu 610041, China
[2]Pituitary Tumor and Related Diseases Diagnosis and Treatment Center, West China Hospital, Sichuan University, Chengdu 610041, China

Corresponding author: YU Yerong, Professor/Doctoral supervisor; E-mail: yerongyu04@scu.edu.cn

Abstract

Pituitary prolactinoma is a neuroendocrine disease caused by excessive synthesis and secretion of prolactin from pituitary lactotroph adenomas. Standardized diagnosis and treatment of pituitary prolactinoma are crucial for restoring and maintaining normal pituitary function and improving patients' quality of life. In January 2022, the International Chapter of Clinical Endocrinology (ICCE) and the Italian Association of Clinical Endocrinologists (AME) published the updated clinical practice consensus statement—the *2022 ICCE/AME Position Statement for Clinical Practice in Pituitary Prolactinoma* (hereinafter referred to as the "2022 ICCE/AME Position Statement"). Based on the latest evidence-based medical evidence, this statement provides systematic review, analysis, and recommendations on the clinical diagnosis and treatment of pituitary prolactinoma. This article interprets the updated key points regarding diagnosis, treatment, special populations, dopamine agonist resistance, and invasive disease from the 2022 ICCE/AME Position Statement, aiming to enhance understanding of pituitary prolactinoma among general practitioners and endocrinologists and provide a reference for standardized clinical practice.

Keywords: Prolactinoma; Pituitary neoplasms; Hyperprolactinemia; Guidebook; Prolactin; Dopamine agonists; Drug therapy

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1. Clinical Characteristics

The clinical symptoms of pituitary prolactinoma include hyperprolactinemia-related syndromes and mass effect-related syndromes. The 2022 ICCE/AME Position Statement notes that clinical manifestations vary depending on gender, age, tumor size, prolactin (PRL) levels, and duration of hyperprolactinemia.

1.1 Hyperprolactinemia-Related Clinical Syndromes

Pituitary prolactinoma predominantly affects young and middle-aged women, with a marked gender disparity (female:male ratio of 10:1). Epidemiological data show that incidence rates become similar in both sexes after age 50.

Female patients typically present with amenorrhea and galactorrhea, while male patients may experience decreased libido, sexual dysfunction, hypogonadism, and secondary symptoms. Notably, erectile dysfunction (ED) is often the earliest clinical manifestation in male patients. Signs such as muscle laxity, sparse pubic hair, receding hairline, slowed beard growth, and small/soft testicles suggest hypogonadism. Some male patients even develop gynecomastia.

Long-term hyperprolactinemia-related hypogonadism can also manifest as secondary sexual characteristic regression, anemia, decreased bone mass, and osteoporosis.

1.2 Mass Effect-Related Clinical Syndromes

Beyond hyperprolactinemia symptoms, pituitary prolactinomas can cause tumor mass effects, including headache, nausea, vomiting, decreased vision or visual field defects, and corresponding clinical symptoms from compression of adjacent structures. Recurrent headaches in prolactinoma patients are often related to tumor growth compressing the diaphragma sellae. Once the tumor breaks through the diaphragma sellae and grows suprasellarly, headaches may partially relieve due to pressure release, but optic chiasm compression can lead to decreased vision or visual field defects, primarily manifesting as temporal or superotemporal hemianopia.

Further tumor growth invading the hypothalamus may cause hypothalamic syndrome with appetite abnormalities, sleep disorders, thermoregulation disturbances, and autonomic nervous dysfunction. Compression of the pituitary stalk can cause central diabetes insipidus with polydipsia and polyuria. Invasion of the cavernous sinus with compression of cranial nerves (III, IV, VI) can cause diplopia, ptosis, ophthalmoplegia, or sensory abnormalities. Compression of normal pituitary hormone-secreting cells (e.g., growth hormone [GH], thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH]) may result in deficiency of one or more anterior pituitary hormones.

Additionally, when pituitary prolactinoma constitutes part of a mixed pituitary adenoma or multiple endocrine neoplasia, patients may present with other pituitary-target gland hormone level abnormalities.

2. Diagnosis

Pituitary prolactinoma diagnosis requires evaluation of clinical symptoms and signs, PRL levels, and sellar/pituitary imaging.

2.1 Hyperprolactinemia

The diagnosis of hyperprolactinemia is established by measuring basal PRL levels, which often correlate with tumor size. PRL levels >200–250 g/L suggest a tumor diameter >1 cm (PRL-secreting macroadenoma). Since PRL is secreted in a pulsatile manner with higher levels during fasting and sleep, and is stimulated by stress, exercise, walking, venipuncture, and protein-rich diets, the 2022 ICCE/AME Position Statement recommends non-fasting measurement with a venous cannula placed 15–20 minutes before blood collection to avoid these influencing factors.

Due to diverse detection methods, clinicians should be aware of the specific PRL assay method and units used. In macroadenomas (e.g., >3 cm diameter) with disproportionately elevated PRL levels, samples with normal or only mildly elevated PRL should be serially diluted to exclude the "hook effect."

The 2022 ICCE/AME Position Statement advises clinicians to obtain detailed medical and medication histories to exclude physiological (including pregnancy, lactation), secondary (such as hepatic dysfunction, renal insufficiency, primary hypothyroidism), and drug-induced hyperprolactinemia (from antihypertensives, gastrointestinal drugs, dopamine receptor antagonists, estrogen-containing oral contraceptives, opioid preparations, H2 receptor blockers, etc.). This aligns with the 2011 US Endocrine Society Guideline and the 2014 Chinese Consensus.

When drug-induced hyperprolactinemia is suspected, PRL should be rechecked 3–4 days after discontinuing the offending medication. The statement does not recommend initial pituitary imaging for suspected drug-induced hyperprolactinemia; sellar/pituitary contrast-enhanced MRI should only be considered if hyperprolactinemia persists after drug discontinuation or substitution. Without definitive diagnosis and appropriate pituitary MRI, dopamine agonist (DA) therapy should not be initiated.

2.2 Sellar Imaging

Sellar MRI is the gold standard for diagnosing pituitary prolactinoma, with dynamic contrast-enhanced imaging facilitating detection of microadenomas. The 2022 ICCE/AME Position Statement recommends careful neuroradiological evaluation to avoid misdiagnosis (false positives). For macroadenoma patients receiving DA therapy, repeat pituitary contrast-enhanced MRI is recommended within 3–6 months, while microadenoma patients can be followed with longer intervals.

Given that gadolinium can be retained long-term in human tissues with debated safety, the 2022 statement recommends limiting gadolinium contrast use in long-term follow-up of prolactinomas (especially macroadenomas), a point not emphasized in previous guidelines.

3. Treatment and Follow-up

DA therapy is first-line treatment for most pituitary prolactinomas, applicable to all tumor sizes including microadenomas ($ $1 cm), macroadenomas (1–4 cm), and giant adenomas (>4 cm). DA can normalize PRL levels in nearly 90% of patients with idiopathic hyperprolactinemia or microadenomas and 75%–80% of macroadenoma patients, with tumor shrinkage observed in most macroadenoma patients during initial treatment.

The most commonly used DAs are bromocriptine and cabergoline. Cabergoline, a novel long-acting ergot derivative, has fewer gastrointestinal adverse effects than bromocriptine with good safety and tolerability. The 2022 ICCE/AME Position Statement recommends cabergoline as first-choice therapy at the lowest effective dose to suppress excessive PRL secretion and reduce tumor volume. It also cautions that cabergoline may cause impulse control disorders, and patients with neuropsychiatric histories should be monitored for psychiatric symptoms.

For patients intolerant to cabergoline or unsuitable for surgery, and in regions where cabergoline is unavailable or scarce, bromocriptine is recommended. Since cabergoline is difficult to obtain in mainland China, bromocriptine—proven safe, effective, accessible, and relatively inexpensive—remains the preferred and commonly used drug, with cabergoline reserved for bromocriptine-resistant cases.

For patients requiring treatment who are unwilling to accept long-term medication, transsphenoidal pituitary surgery (TSS) is an option. TSS is a minimally invasive neurosurgical technique with high cure rates and relatively low complication rates. A recent meta-analysis showed that surgery alone achieved long-term remission in approximately 74% of prolactinoma patients, compared with only 37% who achieved remission after discontinuing medical therapy. In microadenoma patients, postoperative remission rates can be as high as 83%, suggesting surgery as a feasible first-line alternative, particularly for young women with microadenomas.

Radiotherapy is typically reserved for patients with residual or uncontrolled tumors after failed surgery, primarily to control tumor growth, with biochemical remission (PRL normalization) as a secondary goal. Compared with the 2011 US Guideline, the 2022 ICCE/AME Position Statement emphasizes multidisciplinary team (MDT) management, particularly for macro- or giant adenomas.

3.1 Pituitary Prolactin Macroadenomas

Treatment goals for PRL-secreting macroadenomas are rapid relief of neuro-ophthalmic symptoms, PRL level control, and tumor volume reduction. The

2022 ICCE/AME Position Statement recommends cabergoline as first-line therapy regardless of tumor size, even for giant adenomas with severe neurological symptoms, to quickly improve neuro-ophthalmic symptoms under strict clinical and laboratory monitoring.

Surgery should be second-line for invasive adenomas unresponsive to DA. For patients without rapid improvement of severe neuro-ophthalmic deficits within 2 weeks of DA therapy, or those with DA resistance, intolerance, or drug "escape phenomenon" (continued PRL elevation during treatment), adenoma resection by experienced pituitary surgeons is recommended. This aligns with previous guidelines advocating DA as first-line for most macro- or giant adenomas, except for acute tumor apoplexy requiring emergency decompression.

In long-term DA-treated macroadenoma patients, therapy should not be discontinued while tumor persists and PRL levels remain abnormal. Only patients showing complete tumor disappearance (or $ $50% size reduction) and maintained normal PRL levels during gradual DA dose reduction after long-term therapy may consider discontinuation, requiring quarterly monitoring of PRL and pituitary-gonadal axis function.

For invasive macroadenomas responding well to medication, rapid tumor shrinkage may increase cerebrospinal fluid leakage risk, requiring urgent ENT or neurosurgical evaluation if rhinorrhea occurs. Cystic macroadenomas typically do not shrink with DA therapy and may require surgery, especially with persistent visual deficits. For macro- or giant adenomas uncontrolled by DA and surgery, radiotherapy is recommended, with decisions made within a multidisciplinary pituitary team.

3.2 Pituitary Prolactin Microadenomas

Treatment goals for microadenomas are improving clinical manifestations, resolving galactorrhea, and restoring gonadal function and fertility, consistent with the 2011 US Guideline and 2014 Chinese Consensus. In female patients, cabergoline should be administered at the lowest dose maintaining normal menstrual cycles and suppressing galactorrhea. Studies show cabergoline normalizes PRL levels in 73%–96% of hyperprolactinemic patients, with tumor shrinkage observed in >50% of microadenomas.

For patients with mild hypogonadism or galactorrhea symptoms minimally affecting quality of life, clinical observation may be appropriate. For microadenoma women without immediate pregnancy plans, oral estrogen-progestin contraceptives may be considered.

3.3 Osteoporosis

Research demonstrates that DA therapy improves bone mineral density in prolactinoma patients by reducing PRL levels and restoring gonadal axis function, thereby preventing further bone loss and reducing fracture risk. However, the

2022 ICCE/AME Position Statement suggests that osteoporosis may require concurrent treatment using the same regimens as the general population, including lifestyle modifications, calcium and vitamin D supplementation (maintaining serum 25-hydroxyvitamin D within recommended ranges), and anti-osteoporotic drugs including estrogen, calcitonin, bisphosphonates, denosumab, raloxifene, and parathyroid hormone analogs (e.g., teriparatide) to promote bone formation and inhibit resorption.

3.4 Follow-up

For patients with mild disease and no visual impairment, the 2022 ICCE/AME Position Statement recommends that biochemical, ophthalmologic, and neuroradiological follow-up should not be too frequent, with the first assessment at 3–6 months. Subsequent evaluations should be based on clinical course: responsive patients every 6–12 months, and partial responders more frequently (every 3–6 months).

For most severely ill patients, disease control should be achieved in the short term: strict neuro-ophthalmologic examination and clinical assessment within the first month to guide neurosurgical intervention timing; PRL levels should be evaluated weekly or monthly during the first 3 months, with follow-up intervals extended if treatment is effective; repeat MRI should be based on ophthalmologic and PRL level changes.

The 2011 US Guideline suggested that DA therapy could be gradually reduced and stopped after at least 2 years of treatment in patients with normalized PRL levels and no visible tumor residue on MRI. The 2022 ICCE/AME Position Statement, incorporating clinical practice, explicitly states that DA therapy should not be discontinued if PRL levels rise again after dose reduction.

For microadenomas, male patients require lifelong treatment to maintain normal sex hormones, while female patients may discontinue therapy after menopause when estrogen decline leads to spontaneous PRL normalization. Macroadenoma treatment should also be lifelong, though occasional discontinuation attempts may succeed but require follow-up.

4. Special Populations

4.1 Children and Adolescents

The 2022 ICCE/AME Position Statement recommends DA therapy for children with pituitary prolactinoma to protect normal pituitary function and vision, ensuring growth and sexual development. For children or adolescents with DA resistance or intolerance, neurosurgical treatment may be an alternative.

4.2 Pregnant Women

Women with microadenomas may consider pregnancy after PRL levels normalize or near-normalize and regular menstruation resumes. For macroadenoma patients, pregnancy should be considered only after tumor shrinkage to minimize tumor growth risk during pregnancy.

The 2022 ICCE/AME Position Statement recommends that healthcare institutions provide adequate information and accessible endocrinology consultation for pregnant patients with prolactinoma. Multidisciplinary expert teams (endocrinology, neurosurgery, obstetrics, ophthalmology) should discuss treatment risks and benefits to develop individualized plans.

DA therapy (preferably cabergoline for better tolerability) is recommended when planning pregnancy and should be discontinued after pregnancy confirmation. This differs from the 2014 Chinese Consensus, which recommended discontinuation after 12 weeks' gestation for microadenomas and continuous medication during pregnancy for macroadenomas. Since pregnancy itself can elevate PRL levels, PRL monitoring is not recommended during pregnancy, and pituitary MRI should be avoided during stable pregnancy and early postpartum period to prevent potential fetal harm.

Macroadenoma patients should undergo comprehensive clinical, biochemical, pituitary function, and neuro-ophthalmologic assessments during each trimester. Symptomatic macroadenoma patients during pregnancy should undergo gadolinium-free MRI, pituitary function, and neuro-ophthalmologic evaluation. Symptomatic macroadenoma patients should restart DA therapy (preferably cabergoline) to rapidly relieve symptoms, which may be continued postpartum.

Microadenoma patients are recommended for vaginal delivery (unless obstetricians advise otherwise), while delivery mode for macroadenoma patients should be individualized. Stable prolactinoma patients may breastfeed, postponing DA restart. After delivery or breastfeeding cessation, physical contraception should be used to allow PRL level assessment within 3–6 months, with MRI follow-up for macroadenoma patients. Symptomatic hyperprolactinemia recurrence postpartum warrants DA therapy restart.

4.3 Postmenopausal Women

Menopause may benefit the natural course of prolactinoma. Recent clinical studies suggest that PRL levels spontaneously normalize during menopause in untreated microadenoma patients, with some showing tumor disappearance. The 2022 ICCE/AME Position Statement recommends hormone replacement therapy for hypogonadal female prolactinoma patients at least until physiological menopause age.

Postmenopausal women with microadenomas may attempt DA discontinuation, with annual PRL monitoring if levels rise, and pituitary MRI if levels progres-

sively increase. Macroadenoma patients should continue DA postmenopause at the lowest dose controlling tumor growth, with regular follow-up based on clinical status.

All macro- and giant adenoma patients, especially men due to higher instability risk, require strict follow-up. Remission rates are lower for giant or invasive tumors, as endocrine biochemical remission often negatively correlates with adenoma size. Preoperative peak PRL levels and cavernous sinus invasion are prognostic predictors for postoperative biochemical remission.

In cases of DA resistance, drug escape, or uncontrolled tumor growth, the 2022 ICCE/AME Position Statement recommends prompt combination therapy (repeat surgery + radiotherapy + DA). For DA-resistant macroadenoma patients with failed surgery and/or radiotherapy or aggressive growth, the oral alkylating agent temozolomide is recommended. For temozolomide-unresponsive aggressive tumors, experimental approaches such as chemotherapy, immunotherapy, or peptide receptor radionuclide therapy may be used, though efficacy remains uncertain. With deepening understanding of pituitary tumorigenesis and accumulating clinical data, developments in biotherapy may bring new hope for prolactinoma management.

In summary, the 2022 ICCE/AME Position Statement provides evidence-based recommendations for prolactinoma diagnosis, treatment, and special situations, considering micro- vs macroadenomas, gender, patient preferences, fertility desires, DA sensitivity/tolerability, and tumor invasiveness. Compared with the 2011 US Guideline and 2014 Chinese Consensus, the 2022 statement places greater emphasis on patient preference and benefit-risk ratio when selecting treatment options. It stresses multidisciplinary collaboration, such as obstetricians and endocrinologists jointly discussing delivery mode and breastfeeding, and timely MDT referral for complex cases. While providing standardized management guidance, differences in economic and healthcare conditions between China and Western countries warrant adaptation to local contexts.

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