EnM
ENDOCRINOLOGY AND METABOLISM

Review Article

Endocrinol Metab 2024;39:819-826
https://doi.org/10.3803/EnM.2024.2057
pISSN 2093-596X · eISSN 2093-5978

# Elucidating Clinical Queries for Tailored Therapy in Patients with Prolactinoma

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Prolactinomas are the most prevalent type of pituitary neuroendocrine adenomas, primarily affecting women of reproductive age. Unlike other pituitary tumors, the first-line management has traditionally been pharmacological rather than surgical. This preference is due to the effectiveness of dopamine agonists (DAs), which typically reduce tumor size and normalize prolactin levels in most patients. However, this does not imply that there is no room for improvement; the duration of treatment and medication side effects often lead to compliance issues among patients. Recent advances in surgical techniques and molecular biology have paved the way for the development of precision medicine, allowing for more flexible and personalized treatment strategies for prolactinomas. This review aims to enhance clinical decision-making and patient care for endocrinologists by focusing on several key factors: predictive markers of DA sensitivity, clinical characteristics and suitability for transsphenoidal adenomectomy as a potential first-line treatment, factors determining the successful withdrawal of DAs after prolonged use, safety concerns during pre/post-pregnancy and breastfeeding, and determinants of tumor aggressiveness. Through tailored therapy—a patient-focused, multidisciplinary approach—we aim to improve the management of prolactinoma patients.

**Keywords:** Prolactinoma; Precision medicine; Clinical decision-making

## INTRODUCTION

Prolactinomas are the most common type of hormonally active pituitary adenomas and predominantly affect women of reproductive age [1]. Unlike other pituitary tumors, prolactinomas are usually treated with medication as the initial approach. This sets them apart in clinical management, especially within the field of endocrinology, where surgery might be the more typical response for other pituitary disorders. Prolactinomas often manifest with symptoms associated with infertility, underscoring the critical role of endocrine expertise in their management. The intricate interplay between pharmacological treatment and reproductive health issues places endocrinologists at the forefront of managing these cases, emphasizing the necessity for specialized and comprehensive care for affected individuals.

The traditional management of prolactinomas has involved the use of dopamine agonists (DAs) as the first-line treatment. These medications effectively reduce tumor size and normalize

**Received:** 6 June 2024, **Revised:** 4 July 2024, **Accepted:** 9 July 2024

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prolactin levels in most patients [2]. However, variability in the response to DAs and potential side effects pose challenges in clinical practice [3]. In patients with prolactinoma receiving DA treatment, the duration for maintenance of DAs varies, and the recurrence rate is not negligible after cessation of DAs [4]. Advancements in surgical techniques for pituitary tumors, along with increased research in molecular biology on drug responsiveness, have paved the way for the application of precision medicine, both for patients with acromegaly and those with prolactinomas [5]. These developments have improved the accuracy of targeting and managing pituitary diseases. As a result, personalized therapeutic approaches are increasingly viable for patients with prolactinomas, leading to better outcomes and fewer treatment-related complications.

In this review, we have compiled research findings that address key clinical questions endocrinologists face when managing patients with prolactinomas. By focusing on the unique aspects of prolactinomas, we aim to provide evidence-based insights that will improve clinical decision-making and patient care for endocrinologists.

## CAN SENSITIVITY TO DOPAMINE AGONISTS BE PREDICTED?

The standard treatment for treating prolactinomas involves the administration of DAs, such as cabergoline (CAB) and bromocriptine (BRC). These medications are generally effective in normalizing prolactin levels and reducing tumor size. However, despite their efficacy, approximately 10%–20% of patients exhibit resistance, characterized by persistent hyperprolactinemia and/or tumor growth despite maximal DA therapy [6]. Therefore, understanding the mechanisms behind DA sensitivity and resistance is crucial for improving clinical outcomes. Although our understanding of the factors contributing to DA resistance is still incomplete, several retrospective studies have identified promising indicators that may help predict responses to DA treatment in certain scenarios [3,4,7-11]. These studies have explored clinical parameters such as early serum prolactin levels in patients treated with DAs, as well as patient demographics and radiographic characteristics of pituitary tumors on magnetic resonance imaging (MRI) that may be associated with sensitivity to DA treatment.

An important clinical parameter when assessing DA sensitivity is the serum prolactin concentration in patients undergoing DA treatment. Research suggests that measuring serum prolactin levels at 3 months can predict treatment outcomes for many patients. Additionally, prolactin levels after 3 months of treatment initiation can predict long-term responsiveness to DA therapy; levels below 1 ng/mL after this period have been associated with higher DA sensitivity and significant tumor volume reduction [4,9]. These measurements can help differentiate between overt prolactinomas with mild hyperprolactinemia and non-functioning pituitary adenomas with hyperprolactinemia (NFPAH). The treatment strategies for these two types of tumors vary significantly, making early diagnosis crucial for optimal treatment outcomes, especially since prolonged DA treatment has been linked to side effects such as peritumoral fibrosis. Baseline prolactin levels before clinical intervention can also aid in predicting DA sensitivity. Patients with initial prolactin levels typically >200 ng/mL have shown a greater response to DAs, excluding those with atypical giant prolactinoma [8]. Pituitary tumors with lower prolactin levels, particularly those with levels <127 ng/mL, were identified as NFPAH, which may explain the observed DA resistance [7]. A retrospective study conducted by another team also found that monitoring initial prolactin concentrations can provide insights into expected treatment efficacy [12]. Patient demographics have been found to influence DA sensitivity, with studies indicating that younger patients and males are more likely to exhibit DA resistance [13].

Tumor size and invasiveness were also found to affect DA sensitivity; specifically, larger and/or more invasive prolactinomas were found to be more likely to exhibit DA resistance, and MRI findings of substantial tumor mass or cavernous sinus invasion were also associated with resistance to DAs [3,7,14]. Patients with microprolactinomas (less than 10 mm) generally exhibit higher DA sensitivity and better outcomes than those with macroprolactinomas (more than 10 mm) [3,7]. Furthermore, patients with unusually large prolactinomas (tumor size greater than 4 cm) and concurrent hypopituitarism, which necessitates pituitary hormone replacement therapy, face a higher risk of DA resistance and complications, such as cerebrospinal fluid rhinorrhea [8].

Regarding the predictive value of tumor characteristics in MRI, a strong correlation was observed between tumor volume reduction by the third month of CAB treatment and DA sensitivity. A tumor volume reduction of less than 25% suggested DA resistance, indicating that surgery might be a better option since 50% of these patients did not achieve complete remission with CAB alone [9]. Although T2-weighted MRI signal intensities are useful predictors of a tumor's somatostatin responsiveness in growth hormone secreting pituitary adenoma, they failed to demonstrate clinical significance in patients with prolactinoma

[15]. No significant correlation was noted between these MRI signal intensities and DA resistance. Additionally, no discernible landmarks identifiable through visual inspection were correlated with DA resistance. Cystic and hemorrhagic changes observed on MRI also showed no correlation with DA responsiveness. However, in the radiomics approach, the ensemble classifier significantly predicted DA responsiveness in patients with prolactinomas [11]. In a study of 177 prolactinoma patients, radiomic features from baseline MRI were used to predict DA response. A soft voting ensemble classifier outperformed individual models, achieving an area under the curve of 0.81 with 77.8% accuracy, 78.6% sensitivity, and 77.3% specificity in the test set [11].

Since most patients do not undergo surgery, obtaining tumor tissue for molecular studies is challenging. However, it is still possible to conduct research at a molecular level using the small amounts of tissue collected. The efficacy of DAs largely depends on the presence of the dopamine D2 receptor (D2R) on lactotroph cells [16]. Studies have shown that prolactinomas with higher D2R expression respond better to DA treatment. Quantifying D2R expression through immunohistochemistry or mRNA analysis can serve as a predictive marker [14]. G protein-coupled receptor kinase 2 (GRK2) modulates D2R sensitivity [17]. Increased levels of GRK2 have been linked to decreased DA responsiveness due to enhanced D2R desensitization and internalization. Measuring GRK2 expression may help predict the outcomes of DA treatment [13]. Additionally, estrogen receptor alpha (ERα) expression in prolactinomas, which modulates prolactin synthesis and secretion, may affect DA sensitivity. Higher ERα levels could potentially indicate resistance [14]. Finally, epigenetic modifications, including DNA methylation and histone modifications, affect gene expression related to DA sensitivity. Identifying other targets correlated with DA resistance through these approaches could become a cornerstone in personalizing patient treatment strategies [10].

## ARE PREGNANCY AND BREASTFEEDING SAFE IN WOMEN WITH PROLACTINOMAS?

DA treatment restores ovulation in over 90% of women with amenorrhea and anovulation due to prolactinomas [18]. When selecting a DA for women who wish to become pregnant, BRC has traditionally been the preferred choice due to its shorter half-life and the extensive data supporting its use compared to CAB. It is important to note that cumulative data have not shown adverse outcomes with CAB; therefore, both medications are considered effective for use during pregnancy [19,20]. Furthermore, neither drug has been linked to an increased risk of spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations with short-term exposure, generally less than 6 weeks of gestation [21]. Therefore, DAs remain the standard treatment for women with prolactinoma, while surgery prior to pregnancy is still an option for patients who are resistant to DA treatment or do not experience tumor shrinkage despite the normalization of prolactin levels [22].

It is generally recommended that a patient wait for multiple menstrual cycles to take place before attempting to conceive after initiating DA treatment, as this enables better monitoring of missed menstrual cycles [23]. Once pregnancy is confirmed, DA treatments are promptly discontinued in patients with a microadenoma or non-compressive macroprolactinoma, and these patients are then monitored clinically through regular office visits with an endocrinologist. Routine periodic measurements of prolactin levels during pregnancy offer no diagnostic benefits and can be misleading.

Prolactinomas can enlarge during pregnancy due to the stimulatory effect of high estrogen levels and the discontinuation of DA treatment. Significant tumor growth that causes symptoms and requires intervention has been reported in 2.4% of cases with microadenomas, 21% of cases with macroadenomas without prior surgery or irradiation, and 4.7% of cases with macroadenomas with prior surgery or irradiation [24]. If symptoms such as visual field defects or progressive headaches occur, a visual field test and sella MRI without gadolinium should be conducted for patients who require intervention [25]. If significant tumor growth is confirmed, most patients respond well to retreatment with DA. CAB can also be used for the remainder of the pregnancy [26]. Surgical debulking in the second trimester or delivery (if the pregnancy is sufficiently advanced) may be considered if there is no response to DA, although this is rarely necessary [19,27].

Breastfeeding in women with prolactinomas is generally considered safe [27-31]. A previous study showed that there was no significant difference in the remission rate between women who breastfed and those who did not [28]. Lactation had no apparent effect on the growth of pituitary tumors based on radiological and neurological evaluation [29]. A single-center observational study over 10 years also indicated that breastfeeding did not increase the recurrence rate of hyperprolactinemia [31]. If a woman decides to breastfeed, DA treatment can be resumed after

breastfeeding is completed [27].

Interestingly, several studies have suggested that pregnancy may have a favorable effect on prolactinoma due to microhemorrhage and necrosis in the gland during pregnancy [23,31,32]. In a cohort study, pregnancy normalized prolactin levels in two-thirds of patients treated with CAB before gestation [31]. Pregnancy itself appears to improve hyperprolactinemia in women with prolactinoma. Given the spontaneous remission during pregnancy, it is advisable to assess prolactin levels after pregnancy and breastfeeding before making a definitive decision about restarting DAs.

## ARE THERE FACTORS INFLUENCING THE SUCCESSFUL WITHDRAWAL OF DOPAMINE AGONISTS?

Although DAs are highly effective in treating prolactinoma, the optimal timing for discontinuing DA therapy remains controversial. According to the Pituitary Society guidelines, a trial of DA tapering and withdrawal may be considered for patients who meet the following criteria [2]: (1) achievement of normal prolactin levels post-therapy; (2) completion of a 3-year period of DA treatment; and (3) significant reduction in tumor volume. Similarly, the Endocrine Society suggests that it is safe to attempt DA withdrawal after 2 years of treatment in patients who have achieved normal prolactin levels and substantial tumor shrinkage [33].

A previous meta-analysis showed that withdrawal of DAs was associated with persisting normal prolactin levels in only 21% of patients with microprolactinomas and 16% of those with macroprolactinomas [34]. The probability of treatment success is highest when CAB is used for at least 2 years. Another meta-analysis also reported that patients who received the lowest CAB dose and presented a significant reduction in tumor size before withdrawal were most likely to achieve success [35]. Kharlip et al. [36] documented the recurrence of hyperprolactinemia in patients following the cessation of long-term CAB therapy, in accordance with the Pituitary Society guideline. The size of the remaining tumor prior to withdrawal was a critical predictor of recurrence, with 91% of recurrences occurring within 1 year of stopping the treatment [36]. Furthermore, in patients with visible tumors, discontinuing CAB after prolonged therapy significantly increased the risk of recurrent hyperprolactinemia if there was cavernous sinus invasion at the time of diagnosis [15].

A prospective cohort study showed that normalization of MRI findings before discontinuation and the duration of DA treatment were significant predictive factors for the remission of microprolactinoma after DA withdrawal [37]. Colao et al. [38] identified the maximal tumor diameter during treatment with CAB as the best predictor of prolactin levels at the last follow-up visit following withdrawal. Kim et al. [15] found that initial cavernous sinus invasion at diagnosis was linked to an increased recurrence rate after discontinuing CAB in patients with residual prolactinoma. Despite considerable methodological heterogeneity among studies, evidence consistently indicates that a treatment duration of at least 2 years, the achievement of normal prolactin levels, and tumor size at the time of withdrawal are crucial factors in the successful discontinuation of DA.

## IS TRANSSPHENOIDAL ADENOMECTOMY AS A VIABLE ALTERNATIVE FOR THE FIRST-LINE TREATMENT OF PROLACTINOMA?

DAs have been recommended as the first-line treatment for prolactinoma because of their effectiveness in normalizing serum prolactin levels and reducing tumor size. However, the side effects associated with these medications, coupled with the need for prolonged therapy in most patients, have prompted a reconsideration of transsphenoidal adenomectomy (TSA) as a viable primary treatment option [39].

Although DAs like BRC and CAB effectively normalize prolactin levels and reduce tumor size, they are associated with adverse effects such as nausea, vomiting, headache, and dizziness. These side effects lead to the discontinuation of treatment in 5% to 30% of patients. Furthermore, long-term use of high-dose DAs in Parkinson's disease patients has been linked to increased risks of cardiac valve regurgitation, retroperitoneal fibrosis, and pulmonary fibrosis [39]. Given these potential complications, there is growing interest in the effectiveness and safety of TSA as an alternative primary treatment.

In a retrospective cohort study involving 210 prolactinoma patients treated primarily with TSA, 78.1% achieved hormonal remission, and 92.4% experienced complete tumor removal. The remission rate increased to 84.5% among those with completely excised tumors. Predictors of favorable surgical outcomes included smaller tumor size (<1 cm), absence of cavernous sinus invasion, and female sex. Interestingly, higher rates of hormonal remission were observed in patients who had not undergone preoperative DA treatment [39]. On a related note, a retrospective study including only female patients showed that

measuring prolactin levels post-surgery could be useful in predicting outcomes. This study recorded prolactin levels immediately after surgery and noted that levels measured between 6 and 72 hours after the surgical resection of prolactinoma by TSA could predict long-term remission [40].

Moreover, recent advancements in pituitary surgery, including endoscopic techniques, refined instruments, and improved bleeding management, have significantly enhanced the safety and efficacy of TSA. These improvements have made TSA a more attractive option and have led to its reconsideration as a potential first-line treatment for prolactinomas. This is particularly the case for patients with non-invasive tumors smaller than 2 cm, who may achieve high remission rates with minimal complications [39]. Another study highlighted TSA's potential as a first-line treatment, especially for patients with microprolactinoma. The analysis of surgical outcomes showed that total resection was achieved in 100% of Hardy type 1 tumors, accompanied by an endocrinological remission rate of 89.3%. These findings suggest that TSA can be a highly effective primary treatment for patients with non-invasive microprolactinoma [41-43].

A cost-effectiveness analysis conducted in the United States. compared microscopic and endoscopic TSA with medical therapy for treating microprolactinomas. The study suggested that surgical treatment might be a cost-effective alternative to long-term DA therapy, especially given the potential side effects and recurrence rates following DA discontinuation [43].

While DAs remain the first-line treatment for prolactinomas, the notable advancements in TSA techniques and the high success rates in surgical outcomes indicate that TSA could be a viable first-line treatment option for certain patients. TSA should be considered for non-invasive tumors that are smaller than 2 cm and in cases where patients prefer surgery to long-term medication, assuming the procedure is carried out by skilled pituitary surgeons. Further studies are needed to incorporate these findings and refine management strategies for prolactinoma patients, aiming for personalized and effective treatment approaches.

## WHAT ARE THE FACTORS DETERMINING AGGRESSIVENESS?

Prolactinomas are generally considered benign, but their behavior can vary significantly. Some microadenomas respond well to treatment with DAs or surgery, while others may progress into aggressive and malignant tumors with metastases. Recently, prolactinomas have been identified as the second most frequent type of aggressive tumors and carcinomas [3]. Identifying clinical, pathological, and molecular factors is crucial for pinpointing patients with aggressive lactotroph tumors, enabling intensive therapy and rigorous long-term follow-up.

When assessing potential aggressive behavior in prolactinomas, several factors are taken into account. These include high prolactin levels at initial admission, a large tumor diameter on imaging, a poor response to DAs, the necessity for neurosurgery, or an early relapse following hypophysectomy due to rapid tumor growth [44]. However, these factors alone do not conclusively determine the aggressiveness of the tumors. Additional insights are provided by postoperative histological and immunohistochemistry reports. Specifically, a mitotic count greater than 2 and a Ki-67 index of 3% or higher are associated with DA-resistant and invasive prolactinomas [26].

A poor prognosis may also be linked to factors such as male sex, early age at diagnosis, or genetic predisposition. The pituitary tumor-transforming gene (PTTG), a member of the securin family that regulates sister chromatid separation during mitosis, is found to be overexpressed in invasive prolactinomas compared to their non-invasive counterparts [45]. In a study involving 81 patients, clinical and pathological correlations showed that low estrogen receptor expression (immunohistochemistry score <6) was associated with larger tumor size, greater invasion, higher Ki-67 index, increased mitotic count, elevated p53 expression, higher tumor grade (grade 2b), surgical remission, DA resistance, and tumor progression. A comparison between aggressive and non-aggressive prolactinomas identified seven genes (ADAM metallopeptidase with thrombospondin type 1 motif 6 [*ADAMTS6*], collapsin response mediator protein 1 [*CRMP1*], *PTTG*, *ASK*, cyclin B1 [*CCNB1*], aurora kinase B [*AURKB*], and centromere protein E [*CENPE*]) that were associated with invasion, pathological classification, persistence, and disease progression [6]. Furthermore, an inverse correlation was observed between tumor aggressiveness and the expression levels of four microRNAs (miRNAs): miR-183, which acts as an anti-proliferative agent by targeting KIAA0101; miR-340, which targets NIMA related kinase 2 (*NEK2*), *AURKB*, and cyclin B2 (*CCNB2*); miR-744, which targets transforming growth factor beta 1 (*TGFB1*); and miR-98, which targets centromere protein K (*CENPK*), ubiquitin conjugating enzyme E2 T (*UBE2T*), and E2F transcription factor 2 (*E2F2*) [46]. Additional indicators of poor prognosis may include the assessment of E-cadherin, matrix metalloproteinase-9 (*MMP-9*), growth factors such as vascular endothelial growth factor (*VEGF*), and abnormal expression

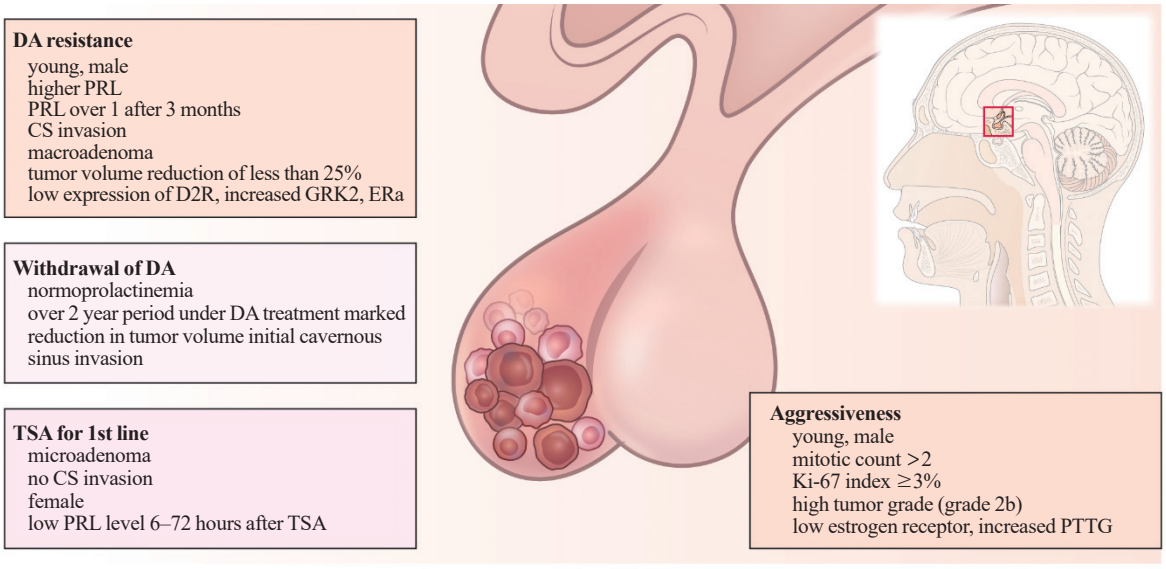


**Fig. 1.** Presentative biomarkers of sensitivity to dopamine agonists in patients with prolactinomas. DA, dopamine agonist; PRL, prolactin; CS, cavernous sinus; D2R, dopamine 2 receptor; GRK2, G protein-coupled receptor kinase 2; ERα, estrogen receptor alpha; TSA, transsphenoidal adenomectomy; PTTG, pituitary tumor-transforming gene.

of genes like aryl hydrocarbon receptor-interacting protein (*AIP*), multiple endocrine neoplasia type 1 (*MEN1*), p53, or even mutations in the breast cancer gene 1 (*BRCA1*).

## CONCLUSIONS

Traditionally, prolactinomas have been uniformly treated with DAs as the primary therapy. However, this review highlights the heterogeneity in patient responses, indicating that some patients exhibit resistance to DAs and may benefit from surgical resection as a first-line treatment, as summarized in Fig. 1. The variability in treatment response underscores the need for personalized therapeutic approaches. Molecular biological characteristics of prolactinoma tissue, as discussed in this review, significantly influence prognosis and treatment outcomes, necessitating tailored treatment strategies based on these molecular markers. Furthermore, obtaining tumor tissue for molecular studies in prolactinoma patients is often not feasible. This limitation emphasizes the importance of identifying non-invasive biomarkers that can be easily obtained from blood samples or MRI to predict treatment response and monitor disease progression. These biomarkers could provide critical insights into the molecular underpinnings of prolactinomas, aiding in the development of personalized treatment plans. By integrating these approaches, clinicians can enhance the precision and efficacy of prolactinoma management, ultimately improving patient outcomes and quality of life.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENTS

As I, Eun Jig Lee, approach my retirement from Yonsei University, I am honored to write a review on tailored therapy, also known as the customized treatment approach, for prolactinoma. Reflecting on my 30-year focus on pituitary tumors, I extend heartfelt thanks to Professor Kap Bum Huh, who has been my mentor throughout this journey, and to Dr. Larry Jameson, whose support has been instrumental in advancing my research. I am also grateful to my colleagues, students, professors, and nurses at the Pituitary Tumor Center at Severance Hospital, Yonsei University College of Medicine, who have collaborated with me over the past decade. Their names are Cheol Ryong Ku, Sun Ho Kim, Se Hoon Kim, Seung-Koo Lee, and Hae Won Kim. I sincerely hope that the insights gained from our clinical experiences and translational research, as described in this review, will benefit those treating prolactinoma.

The study received support from the "Team Science Award" of Yonsei University College of Medicine (6-2022-0150). Med-

ical Illustration & Design (MID), part of the Medical Research Support Services at Yonsei University College of Medicine, provided outstanding support with medical illustration.

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