

## CLINICAL CASE SEMINAR

# The Novel Use of Very High Doses of Cabergoline and a Combination of Testosterone and an Aromatase Inhibitor in the Treatment of a Giant Prolactinoma

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**Most prolactinomas respond rapidly to low doses of dopamine agonists. Occasionally, stepwise increases in doses of these agents are needed to achieve gradual prolactin (PRL) reductions. Approximately 50% of treated men remain hypogonadal, yet testosterone replacement may stimulate hyperprolactinemia.**

**A 34-yr-old male with a pituitary macroadenoma was found to have a PRL level of 10,362  $\mu\text{g/liter}$  and testosterone level of 3.5 nmol/liter. Eleven months of dopamine agonist therapy at standard doses lowered PRL levels to 299  $\mu\text{g/liter}$ . Subsequent stepwise increases in cabergoline (3 mg daily) further lowered PRL levels to 71  $\mu\text{g/liter}$ , but hypogonadism persisted. Initiation of testosterone replacement resulted in a rise and dis-**

**continuation in a fall of PRL levels. Aromatization of exogenous testosterone to estradiol and subsequent estrogen-stimulated PRL release was suspected. Concomitant use of cabergoline with the aromatase inhibitor anastrozole after resuming testosterone replacement resulted in the maintenance of testosterone levels and restoration of normal sexual function, without increasing PRL. Ultimately, further reduction in PRL on this therapy permitted endogenous testosterone production. Thus, novel pharmacological maneuvers may permit successful medical treatment of some patients with invasive macroprolactinomas. (*J Clin Endocrinol Metab* 87: 4447–4451, 2002)**

Therapy with dopamine agonists such as bromocriptine and cabergoline has proven to be highly effective treatment for prolactinomas, both in reducing hyperprolactinemia and inducing tumor shrinkage (1–3). The majority of micro- and macroprolactinomas respond to low doses of dopamine agonists with a rapid lowering of prolactin (PRL) within hours of administration of these drugs (4). In addition to their rapid PRL-lowering effects, bromocriptine and cabergoline are capable of inducing significant tumor shrinkage within the first 3 months of therapy in the majority of tumors (4, 5).

Some prolactinomas, however, demonstrate a relative resistance to dopamine agonists and require escalating doses of these agents to elicit satisfactory responses. Although not widely appreciated or recognized, a subset of prolactinomas respond only with a stepwise reduction in PRL levels with continued stepwise increases in the dose of dopamine agonist therapy. These more gradual responses have been observed in several published trials evaluating the efficacy of dopamine agonists in the treatment of prolactinomas. For example, in a study of 23 patients with macroprolactinomas treated with cabergoline, 70% of patients achieved a normal PRL level within 12 wk of instituting therapy, and 83% achieved a normal PRL level within 6 months (3). PRL levels in the remaining 17% of patients were reduced to a range of mildly elevated values by increasing doses of cabergoline to

3 mg/wk. In another series of 56 patients with macroprolactinomas treated with cabergoline, 82% achieved normal PRL levels within the first 6 months of therapy. In the remaining 18% of patients, cabergoline doses were increased to a maximum of 7 mg/wk over 12 months, allowing an 88% reduction of initial PRL levels (6).

Cabergoline in particular has been shown to be effective in normalizing PRL levels in patients with macroprolactinomas resistant to bromocriptine or quinagolide (CV205–502). In a study of 19 patients with macroprolactinomas deemed resistant to bromocriptine or quinagolide, cabergoline in weekly doses of 0.5–3.0 mg normalized PRL levels in 47% of patients within 1–6 months, in another 16% by 12 months, and in another 11% after 18 months (7). However, the successful use of very large doses of cabergoline (beyond 7 mg weekly) in the treatment of resistant prolactinomas has not been reported.

Moreover, hypogonadism persists in 50% of men with macroprolactinomas, requiring exogenous androgen replacement (5, 8, 9). Although testosterone replacement will normalize serum testosterone levels, sexual dysfunction may persist in some of these patients (9–11). We report a patient with a pituitary incidentaloma that turned out to be a giant macroprolactinoma. This patient required stepwise escalations to very high doses of cabergoline to reduce PRL levels in a stepwise pattern. In addition, an aromatase inhibitor was used in conjunction with testosterone injections to facilitate androgen replacement. The combination of very high doses

Abbreviations: MRI, Magnetic resonance imaging; PRL, prolactin.

of cabergoline, testosterone injections, and an aromatase inhibitor permitted near normalization of PRL levels and eventual recovery of the patient's endogenous gonadal axis. We believe that this case experience provides ideas for new therapeutic strategies for treatment of patients with macroprolactinomas.

### Patients and Methods

#### *Hormone measurements and magnetic resonance imaging (MRI)*

Plasma PRL, LH, FSH, estradiol, testosterone, and  $T_4$  levels were measured through Quest Diagnostics, Inc. by RIA methods. The normal range for PRL is 2.7–12.2  $\mu\text{g}/\text{liter}$ , for total testosterone is 9.0–34.7 nmol/liter, for TSH is 0.39–4.60 mIU/liter, and for  $T_4$  is 58–157 nmol/liter. Goldmann perimetry evaluation of visual fields was performed. MRI of the pituitary gland was performed with high resolution T1 weighted images in the sagittal, coronal, and axial planes pre- and postgadolinium enhancement. The first MRI preceded dopamine agonist therapy, the second was performed 5 months later, and yearly exams followed thereafter.

#### *Patient history*

A 34-yr-old previously healthy male presented with symptoms of left-sided hearing loss. To evaluate for the possibility of an acoustic neuroma, an MRI of the brain was performed. This study incidentally demonstrated a giant, invasive pituitary mass measuring 4.5 cm in width, 3.5 cm in sagittal diameter, and 4.5 cm in height (Fig. 1). The tumor occupied the entire sella, extending back along the clivus to the midbrain and into both cavernous sinuses, encasing both internal carotid arteries. The mass extended superiorly to abut the optic chiasm. Visual fields were normal by Goldmann perimetry.

Retrospectively, the patient had noted symptoms of low libido and situational sexual dysfunction for several years. His physical examination revealed the presence of gynecomastia. He had normal visual fields, normal secondary sexual characteristics, and no galactorrhea.

Initial laboratory data revealed a PRL level of 10,362  $\mu\text{g}/\text{liter}$ , an LH of 1 IU/liter, an FSH of 2 IU/liter, and a total testosterone of 3.5 nmol/

liter. The serum total  $T_4$  was 118 nmol/liter, and TSH was 2.21 mIU/liter. The remainder of anterior pituitary function testing was normal.

### Results

Bromocriptine therapy was initiated at 2.5 mg daily and then gradually increased. However, even on 30 mg/d, the PRL level remained elevated at 469  $\mu\text{g}/\text{liter}$ . Therefore, 7 months later, cabergoline was substituted at escalating doses beginning with 1 mg/wk. Over the next 8 months, stepwise increases in cabergoline doses led to stepwise reductions in PRL levels, yielding a level of 88  $\mu\text{g}/\text{liter}$  at a dose of 9 mg/wk (Fig. 2). A repeat MRI of the pituitary showed an approximately 5–10% reduction in tumor size after 10 months of cabergoline therapy when the PRL level was 98  $\mu\text{g}/\text{liter}$ .

Although substantial lowering of PRL levels was achievable with this therapy, gonadal and sexual function did not recover. At 16 months of dopamine agonist therapy, the patient began testosterone replacement with 200 mg enanthate im every 2 wk. Simultaneously, the cabergoline dose was raised to 14 mg/wk. After two injections, PRL rebounded to 113  $\mu\text{g}/\text{liter}$ . Testosterone replacement was discontinued, and the cabergoline dose was raised to 21 mg/wk. Over the next 3 months, PRL levels fell to 71  $\mu\text{g}/\text{liter}$ .

At 22 months of dopamine agonist treatment, when the PRL level was 79  $\mu\text{g}/\text{liter}$ , testosterone replacement was reinitiated. PRL levels again rebounded to 148  $\mu\text{g}/\text{liter}$  after 2 months of testosterone replacement, followed by a gradual rise to 295  $\mu\text{g}/\text{liter}$  over the following 12 months. During this interval, the cabergoline dose was varied between 14 and 21 mg/wk, but no clear dose response effect was observed. To test whether the administration of testosterone was associated with this rise, the testosterone injections were discon-

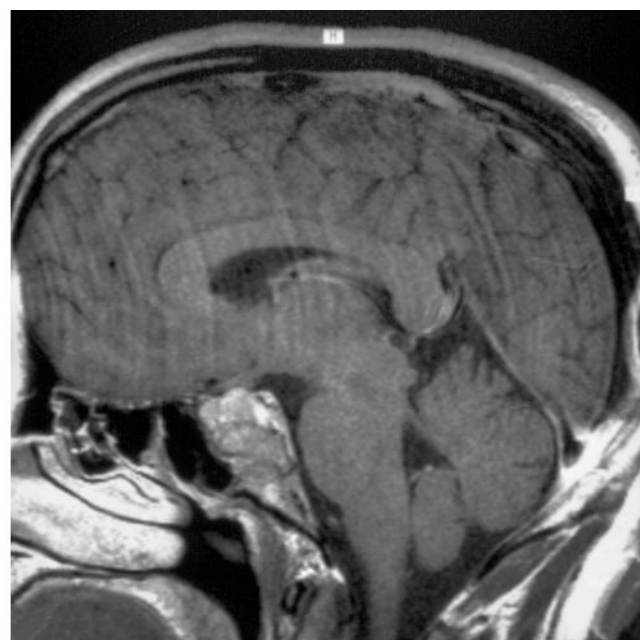
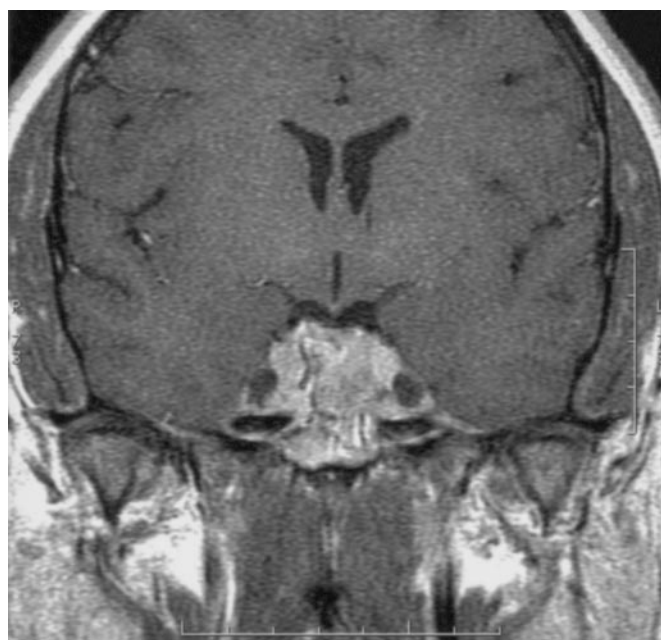


FIG. 1. MRI of the pituitary gland in coronal (A) and sagittal (B) views before initiation of dopamine agonist therapy. The adenoma extends into both cavernous sinuses and encases both internal carotid arteries. The mass is in contact with but does not compress the optic chiasm. Repeated imaging after the introduction of dopamine agonist therapy on a yearly basis has revealed mild (~10%) reduction in tumor size.

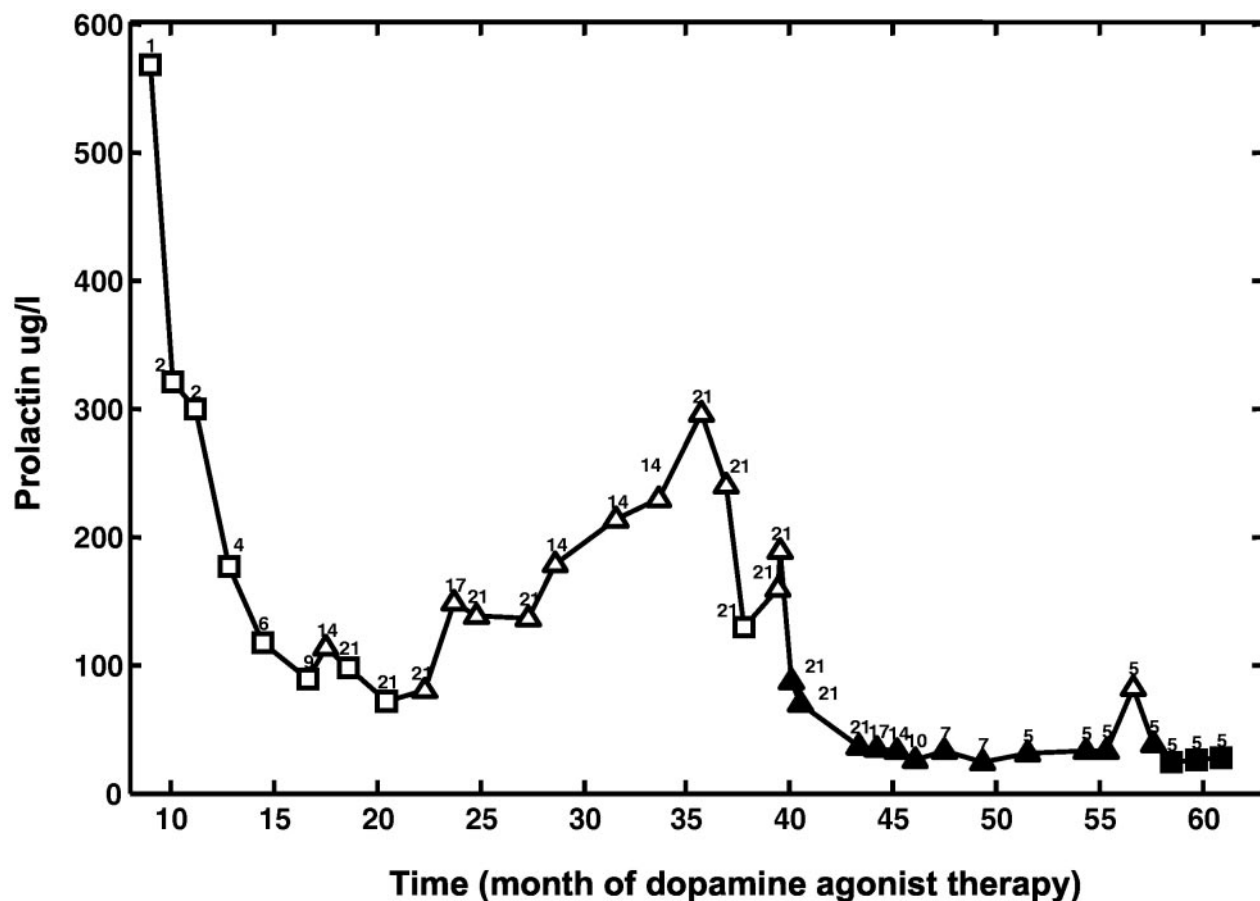


FIG. 2. Graph illustrating PRL levels over time in response to various therapeutic interventions. Cabergoline doses (in milligrams per week) are indicated by the numbers adjacent to symbols. The stepwise reduction in PRL levels associated with escalating doses of cabergoline is demonstrated over the first 22 months of dopamine agonist therapy. Filled symbols indicate concomitant use of aromatase inhibitor therapy. □, Cabergoline therapy alone; △, testosterone plus cabergoline therapy; ▲, testosterone, cabergoline, plus aromatase inhibitor therapy; ■, cabergoline plus aromatase inhibitor therapy.

continued for 6 wk. PRL levels declined after the hiatus in testosterone treatment (months 35–37) and then rebounded to 180  $\mu\text{g}/\text{liter}$  after treatment was reinitiated.

At 39 months, testosterone therapy was supplemented with a selective aromatase inhibitor, anastrozole (Arimidex, AstraZeneca, London, UK), at 1 mg daily. PRL dropped to 86  $\mu\text{g}/\text{liter}$  after 2 wk of anastrozole administration and fell to 36  $\mu\text{g}/\text{liter}$  over the next 3 months. The patient did not suffer any adverse effects from taking either anastrozole or high doses of cabergoline.

Beginning at 43 months of dopamine agonist therapy, 4 months after starting therapy with anastrozole, cabergoline doses were gradually reduced from 21 mg/wk to 5.5 mg/wk over a 6-month time interval without any associated rise in PRL. At 54 months, the patient attempted to discontinue anastrozole as a test to determine whether the aromatase inhibitor continued to provide additional PRL-lowering benefits. The PRL level immediately spiked to 82  $\mu\text{g}/\text{liter}$ , leading to reinstitution of anastrozole and a subsequent decline in PRL back to 37  $\mu\text{g}/\text{liter}$ . At 57 months (after 18 months of anastrozole), testosterone injections were halted. Testosterone levels initially declined, but rose back into the normal range by 59 months. Currently, the patient is taking 5.5 mg

cabergoline per week and 1 mg anastrozole per day. His PRL level has remained below 30  $\mu\text{g}/\text{liter}$  since halting testosterone injections. His total testosterone is 11.1 nmol/liter, and sexual function is now normal.

### Discussion

Most prolactinomas respond to dopamine agonist therapy with rapid reductions of hyperprolactinemia and tumor size within the first several months of therapy. As illustrated by this case, a minority of tumors (often giant prolactinomas) require larger than the conventional doses of dopamine agonists and continue to respond to increasing doses at an appreciable rate even after years of medical therapy (4, 5).

Although cabergoline has been shown to be effective in normalizing PRL levels in some macroprolactinomas resistant to other agents, approximately 25% of these resistant tumors still do not achieve PRL normalization when standard maximal doses are used (7). In one series, 16 patients with resistant prolactinomas were treated with doses of cabergoline as high as 7 mg/wk; however, additional PRL-lowering benefits were not observed beyond total weekly doses of 3.5 mg (6). The effectiveness of even higher doses in

treating resistant prolactinomas has not been systematically investigated.

In this patient, a clear dose response effect between cabergoline dose and PRL level was observed up to a total weekly dose of 9 mg cabergoline in the absence of testosterone and aromatase inhibitor therapy. Doses up to 21 mg/wk may have provided additional PRL-lowering benefits; however, due to simultaneous manipulations in cabergoline dosing and administration of testosterone, the evidence for this is not conclusive. The use of such very large doses of cabergoline has not been previously reported in the treatment of prolactinomas; however, we were reassured with the safety of this approach because doses of cabergoline as high as 5 mg/d have been used for the treatment of Parkinson's disease without major adverse effects (12, 13). The favorable response in our patient indicates that these large cabergoline doses may be safe, tolerable, and effective in the treatment of macroprolactinomas that have relative resistance to dopamine agonists.

Despite the effectiveness of dopamine agonists in attenuating hyperprolactinemia and inducing tumor shrinkage, hypogonadism persists in up to 50% of cases of males with macroprolactinomas, even in individuals in whom PRL levels are normalized (5, 8, 9). Consequently, androgen replacement is required in many of these patients. In general, testosterone replacement is straightforward; however, testosterone replacement in this case was associated with secondary elevations in PRL levels. Evidence for the causal relationship between testosterone replacement and a rise in PRL was suggested by the observation that PRL levels declined when testosterone was temporarily discontinued and rose again with its readministration. We postulate that the rise in PRL was a result of the aromatization of testosterone to estradiol, which in turn stimulated PRL synthesis and release. An accumulating body of evidence suggests that estrogen plays an integral role in the pathogenesis and progression of lactotroph tumors (14). Specifically, estrogen exerts a stimulatory effect upon PRL secretion by disrupting the inhibitory influence of dopamine; chronic exposure to estrogen functionally uncouples the anterior pituitary D2 receptor from its G protein-coupled receptor (15). Estradiol *in vitro* stimulates PRL gene transcription and prevents the ability of dopamine agonists to inhibit PRL synthesis and secretion (16–20). *In vivo*, large doses of estrogens have induced prolactinomas in rats and may induce them in humans as well (21–23).

The frequency of testosterone-associated increases in PRL levels is unknown, because it has not been formally addressed by any of the major trials evaluating dopamine agonist therapy in the treatment of males with macroprolactinomas who subsequently receive androgen replacement. In the only other report in the literature that describes this phenomenon, Prior *et al.* (24) reported a patient with a 6-cm invasive macroprolactinoma (initial PRL, 13,969  $\mu\text{g/liter}$ ) who responded to bromocriptine with a 63% reduction in PRL levels and the disappearance of his visual field defect. Testosterone replacement was followed by visual field deterioration, increased tumor size, and return of PRL levels to baseline values. Indeed, this dramatic response is highly unusual. Testosterone replacement in the patient reported

here led to a more modest PRL rise. Nevertheless, the response was clinically significant because it required the introduction of a second agent (anastrozole) to ultimately attenuate this effect. A study that specifically analyzes PRL responses after testosterone replacement in hypogonadal males with prolactinomas would be necessary to determine whether this response is a unique behavioral characteristic of rare prolactinomas or is one that is observed more commonly.

In the present case, the use of an aromatase inhibitor in conjunction with cabergoline facilitated testosterone replacement, because it prevented the secondary rise in PRL and, ultimately, the potential for tumor enlargement. The aromatase inhibitor was specific for this effect, because discontinuation of anastrozole again led to rises in PRL levels. Interestingly, PRL levels reached their nadir during the period of aromatase inhibitor therapy. These levels were lower than at any other time point, including the period during which the patient was taking his maximum dose of cabergoline (21 mg/wk) without receiving testosterone. This suggests that further lowering of even relatively low levels of estradiol appears to have been beneficial. Consequently, the coadministration of very high doses of cabergoline with anastrozole may have permitted PRL levels to remain low for a duration sufficient to restore the normal pulsatility of GnRH. This in turn led to recovery of the endogenous gonadal axis.

An alternative explanation for the recovery of endogenous testosterone production in this patient may relate to the powerful effect of estradiol deficiency on stimulation of GnRH neurons. Several recent studies have confirmed the observation that lack of estradiol serves as a more potent stimulator of gonadotropin secretion than testosterone deficiency on a molar basis, at both the hypothalamic and pituitary level (25–29).

Short-term administration of aromatase inhibitors has not been associated with adverse effects upon protein or intermediary metabolism or a negative impact on body composition, muscle strength, or measures of bone turnover in healthy eugonadal men (30). However, the long-term effects of aromatase inhibitors are uncertain. As observed in men afflicted with mutations in cytochrome p450 aromatase enzyme or in the estrogen receptor  $\alpha$  gene, chronic estrogen deficiency may have important clinical implications (31). In these individuals, estrogen deficiency has been associated with abnormal carbohydrate/lipid metabolism, abnormal skeletal development, disordered gonadotropin secretion, and infertility. Whether these effects would similarly develop in postpubertal males is not known.

In summary, this case illustrates several intriguing aspects of the management of a giant prolactinoma demonstrating relative dopamine agonist resistance, including 1) the stepwise reduction in PRL levels afforded by stepwise increases in cabergoline to very high doses; 2) the disproportionate degree of pituitary tumor shrinkage despite a dramatic lowering of PRL levels; 3) the facilitation of testosterone replacement by an aromatase inhibitor; and 4) eventual recovery of endogenous gonadal function. Extraordinary pharmacological maneuvers may permit successful medical treatment of some patients with invasive macroprolactinomas.

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## References

- Verhelst J, Abs R, Maiter D, van den Bruel A, Vandeweghe M, Velkeniers B, Mockel J, Lamberigts G, Petrossians P, Coremans P, Mahler C, Stevenaert A, Verlooy J, Raftopoulos C, Beckers A 1999 Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *J Clin Endocrinol Metab* 84:2518–2522
- Biller BM, Molitch ME, Vance ML, Cannistraro KB, Davis KR, Simons JA, Schoenfelder JR, Klubanski A 1996 Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. *J Clin Endocrinol Metab* 81:2338–2343
- Colao A, Di Sarno A, Landi ML, Cirillo S, Sarnacchiaro F, Faccioli G, Pivonello R, Cataldi M, Merola B, Annunziato L, Lombardi G 1997 Long-term and low-dose treatment with cabergoline induces macroprolactinoma shrinkage. *J Clin Endocrinol Metab* 82:3574–3579
- Molitch ME 2001 Disorders of prolactin secretion. *Endocrinol Metab Clin North Am* 30:585–610
- Bevan JS, Webster J, Burke CW, Scanlon MF 1992 Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev* 13:220–240
- Di Sarno A, Landi ML, Cappabianca P, Di Salle F, Rossi FW, Pivonello R, Di Somma C, Faggiano A, Lombardi G, Colao A 2001 Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab* 86:5256–5261
- Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo G, Merola B, Annunziato L, Lombardi G 1997 Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. *J Clin Endocrinol Metab* 82:876–883
- Molitch ME, Elton RL, Blackwell RE, Caldwell B, Chang RJ, Jaffe R, Joplin G, Robbins RJ, Tyson J, Thorne MO 1985 Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. *J Clin Endocrinol Metab* 60:698–705
- Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klubanski A 2000 Primary medical therapy of micro- and macroprolactinomas in men. *J Clin Endocrinol Metab* 85:3053–3057
- Carter JN, Tyson JE, Tolis G, Van Vliet S, Faiman C, Friesen HG 1978 Prolactin-screening tumors and hypogonadism in 22 men. *N Engl J Med* 299:847–852
- Murray FT, Cameron DF, Ketchum C 1984 Return of gonadal function in men with prolactin-secreting pituitary tumors. *J Clin Endocrinol Metab* 59:79–85
- Lera G, Vaamonde J, Rodriguez M, Obeso JA 1993 Cabergoline in Parkinson's disease: long-term follow-up. *Neurology* 43:2587–2590
- Hutton JT, Koller WC, Ahlskog JE, Pahwa R, Hurtig HI, Stern MB, Hiner BC, Lieberman A, Pfeiffer RF, Rodnitzky RL, Waters CH, Muentner MD, Adler CH, Morris JL 1996 Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology* 46:1062–1065
- Heaney AP, Fernando M, Melmed S 2002 Functional role of estrogen in pituitary tumor pathogenesis. *J Clin Invest* 109:277–283
- Munemura M, Agui T, Sibley DR 1989 Chronic estrogen treatment promotes a functional uncoupling of the D2 dopamine receptor in rat anterior pituitary gland. *Endocrinology* 124:346–355
- Gooren LJ, van der Veen EA, van Kessel H, Harmsen-Louman W, Wiegel AR 1984 Prolactin secretion in the human male is increased by endogenous oestrogens and decreased by exogenous/endogenous androgens. *Int J Androl* 7:53–60
- Maurer RA 1982 Relationship between estradiol, ergocryptine, and thyroid hormone: effects on prolactin synthesis and prolactin messenger ribonucleic acid levels. *Endocrinology* 110:1515–1520
- Raymond V, Beaulieu M, Labrie F, Boissier J 1978 Potent antidopaminergic activity of estradiol at the pituitary level on prolactin release. *Science* 200:1173–1175
- West B, Dannies PS 1980 Effects of estradiol on prolactin production and dihydroergocryptine-induced inhibition of prolactin production in primary cultures of rat pituitary cells. *Endocrinology* 106:1108–1113
- Seyfred MA, Klade MP, Gorski J 1989 Transcriptional regulation by estrogen of episomal prolactin gene regulatory elements. *Mol Endocrinol* 3:305–314
- Gooren LJ, Assies J, Asscheman H, de Slegte R, van Kessel H 1988 Estrogen-induced prolactinoma in a man. *J Clin Endocrinol Metab* 66:444–446
- Kovacs K, Stefanescu L, Ezzat S, Smyth HS 1994 Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration. A morphologic study. *Arch Pathol Lab Med* 118:562–565
- Serri O, Noisieux D, Robert F, Hardy J 1996 Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. *J Clin Endocrinol Metab* 81:3177–3179
- Prior JC, Cox TA, Fairholm D, Kostashuk E, Nugent R 1987 Testosterone-related exacerbation of a prolactin-producing macroadenoma: possible role for estrogen. *J Clin Endocrinol Metab* 64:391–394
- Finkelstein JS, Whitcomb RW, O'Dea LS, Longcope C, Schoenfeld DA, Crowley Jr WF 1991 Sex steroid control of gonadotropin secretion in the human male. I. Effects of testosterone administration in normal and gonadotropin-releasing hormone-deficient men. *J Clin Endocrinol Metab* 73:609–620
- Finkelstein JS, O'Dea LS, Whitcomb RW, Crowley Jr WF 1991 Sex steroid control of gonadotropin secretion in the human male. II. Effects of estradiol administration in normal and gonadotropin-releasing hormone-deficient men. *J Clin Endocrinol Metab* 73:621–628
- Bagatell CJ, Dahl KD, Bremner WJ 1994 The direct pituitary effect of testosterone to inhibit gonadotropin secretion in men is partially mediated by aromatization to estradiol. *J Androl* 15:15–21
- Hayes FJ, Seminara SB, Decruz S, Boepple PA, Crowley Jr WF 2000 Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feedback. *J Clin Endocrinol Metab* 85:3027–3035
- Schnorr JA, Bray MJ, Veldhuis JD 2001 Aromatization mediates testosterone's short-term feedback restraint of 24-hour endogenously driven and acute exogenous gonadotropin-releasing hormone-stimulated luteinizing hormone and follicle-stimulating hormone secretion in young men. *J Clin Endocrinol Metab* 86:2600–2606
- Mauras N, O'Brien KO, Klein KO, Hayes V 2000 Estrogen suppression in males: metabolic effects. *J Clin Endocrinol Metab* 85:2370–2377
- Grumbach MM, Auchus RJ 1999 Estrogen: consequences and implications of human mutations in synthesis and action. *J Clin Endocrinol Metab* 84:4677–4694