0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(4):1704–1711

doi: 10.1210/jc.2003-030979

Outcome of Cabergoline Treatment in Men with Prolactinoma: Effects of a 24-Month Treatment on Prolactin Levels, Tumor Mass, Recovery of Pituitary Function, and Semen Analysis

ANNAMARIA COLAO, GIOVANNI VITALE, PAOLO CAPPABIANCA, FRANCESCO BRIGANTI, ANTONIO CICCARELLI, MICHELE DE ROSA, STEFANO ZARRILLI, AND GAETANO LOMBARDI

Department of Molecular and Clinical Endocrinology and Oncology (A.Co., G.V., A.Ca., M.D.R., S.Z., G.L.), Neurological Sciences, and Sections of Neurosurgery (P.C.) and Neuroradiology (F.B.), Federico II University of Naples, 80131 Naples, Italy

The outcome of 24 months of cabergoline treatment on prolactin (PRL) normalization, tumor shrinkage, restoration of pituitary function, and semen alterations was prospectively investigated in 41 men with macro- (age 17–70 yr) and 10 with microprolactinoma (age 18–53 yr). Fifty-one age-matched men served as controls for semen analysis.

At study entry, of the 41 patients with macroprolactinoma, 17 (41.4%) had visual field defects, 14 (34.1%) had headache, eight (19.5%) had galactorrhea, 22 (53.6%) had hypopituitarism apart from hypogonadism, and 30 (73.2%) had low testosterone levels; of the 10 patients with microprolactinoma, none had visual field defects, galactorrhea, or hypopituitarism apart from hypogonadism, two had headache (20%), and five had low testosterone levels (50%; $P = 0.3$).

After 24 months of therapy, 1) PRL levels normalized in 31 patients with macro- (75.6%) and in eight with microprolactinoma (80%; $P = 0.9$), and galactorrhea disappeared in all patients; 2) maximal tumor diameter reduced by 73.7 ± 22.6% in macro- and 72.8 ± 28.3% in microprolactinomas ($P = 0.91$), and 15 macro- (30%) and seven microprolactinomas (46.7%; $P = 0.37$) disappeared; 3) visual field defects disappeared in 15 (75%) patients with macroprolactinoma, and headache disappeared in 15 (83%) patients with macro- and in one with microprolactinoma (50%); 4) GH secretion recovered in 62.5% and ACTH secretion in 60% of patients; 5) testosterone levels normalized in 25 patients with macro- (60.9%) and six with microprolactinoma (60%) after 6 months, and 20 patients required testosterone or gonadotropin replacement (in 14 or six patients, respectively); and 6) sperm volume and count normalized in all patients who normalized testosterone levels, whereas motility normalized in more than 80%. Cabergoline therapy was well tolerated; only 4.5% of patients had side effects at high doses.

These data demonstrate that cabergoline treatment is as effective and safe in men as in women with prolactinoma and can be successfully used as primary therapy even in men bearing large macroprolactinomas. (*J Clin Endocrinol Metab* 89: 1704–1711, 2004)

CLINICAL MANIFESTATIONS AND response to therapy of prolactinomas in women are widely described, whereas scant data are still available in men. This is due mainly to the fact that microadenomas, the most common form of hyperprolactinemia, are more common in women (1), whereas macroadenomas, which are less frequent than microadenomas, were reported to be similarly frequent in either gender (1–4) or more common in men (5, 6). Whether this reflects only a delay in diagnosis in men or a true gender difference in tumor pathogenesis is still unclear, but some data suggest that men could have more aggressive prolactinomas than women (7, 8) and thus are likely less responsive to pharmacotherapy. However, data on hyperprolactinemia in men are still limited compared with women and have usually been analyzed in small retrospective studies (7–18). In a 5-yr prospective study on 219 patients with hyperprolactinemia, we showed that prolactin (PRL) normalization after a 6-month treatment with cabergoline, a D_2-selective dopamine agonist, was higher in micro- than in macroprolactinomas but was similar in women and in men (1). Moreover, scant data are available on the recovery of sperm function in men with prolactinoma. In previous studies including a small cohort of patients (19, 20), we found a significant increase of number, motility at first hour, forward progression, and normal morphology of sperm after either bromocriptine, quinagolide, or cabergoline treatments but improvement of sperm and sexual function was more evident and rapid in patients treated with cabergoline (20). These data were further confirmed in a recent prospective study including 51 patients (21).

To extend our preliminary observation and provide additional details on long-term cabergoline treatment outcome in men with prolactinoma, we prospectively investigated the efficacy of increasing doses of cabergoline on PRL normalization, tumor shrinkage, recovery of visual field and/or other neurological defects, and restoration of pituitary function and sperm function.

Subjects and Methods

Subjects

From 1996–2000, 73 consecutive newly diagnosed men were admitted to our department for hyperprolactinemia, and 51 of them agreed to

Abbreviations: CV, Coefficient of variation; IRMA, immunoradiometric assay; MRI, magnetic resonance imaging; PRL, prolactin.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

be included in this study after their informed consent had been obtained (Table 1). Inclusion criteria were, for macroprolactinomas, serum PRL levels at least 200 μg/liter and a pituitary tumor at least 1 cm in diameter on pituitary magnetic resonance imaging (MRI), and for microprolactinomas, serum PRL levels at least 50 μg/liter and a pituitary tumor less than 1 cm in diameter, with a follow-up of at least 2 yr (1). At study entry, all patients suffered from libido impairment, whereas reduced sexual potency and infertility were referred by some of them (Table 1). After 6 months of beginning treatment, 17 patients (16 macro- and one microprolactinoma) required testosterone replacement and were thus excluded from subsequent follow-ups of semen analysis. For this endpoint only, we thus investigated 25 men with macro- and nine with microprolactinoma at the 12- and 24-month evaluation. Fifty-one men randomly recruited among clerks, students, and doctors age matched with the study population, living in the same geographical area, and without any known disease agreed to serve as controls. All the 51 patients had been included in a previous study reporting only the results of the 6-month follow-up for PRL levels and tumor shrinkage (1). Five patients were also included in the study focusing on tumor shrinkage in macroprolactinomas (22), and six patients with macro- and three with microprolactinoma were included in the study focusing on therapy resistance (2). None of them had been included in previous studies on seminal fluid analysis (19, 20).

Study protocol

At study entry, serum PRL levels were calculated as the average value of a 6-h profile by blood sampling every 30 min (0800–1400 h). After 1, 3, 6, 12, 18, and 24 months of treatment, PRL levels were assayed between 0800 and 0900 h every 15 min for at least three samples, and the average value was taken for statistical analysis. A general clinical examination was performed, and serum FSH, LH, and testosterone were determined before treatment and every 6 months during the follow-up. Additionally, the following symptoms and signs were specifically investigated in all patients: visual field defects, visual loss, headache, galactorrhea, libido and/or potency sexual dysfunction, and infertility. Patients with hypopituitarism received standard replacement therapy with L-thyroxin (50–100 μg by mouth daily) and cortisone acetate (25–37.5 mg/d). Testosterone or gonadotropin replacement, according to the individual patient's desire of fertility, was considered only after 6 months of treatment if testosterone secretion was not normalized. At baseline, GH deficiency was diagnosed by IGF-I levels below the 25th percentile for sex and age, whereas after 6 months of treatment, all subjects were tested with an arginine (ARG) + GHRH test according to Ghigo *et al.* (23). ARG (arginine hydrochloride) was administered at the dose of 0.5 g/kg, up to a maximal dose of 30 g slowly infused from time 0–30 min, whereas GHRH 1–29 was given at the dose of 1 μg/kg as an iv bolus at time 0. Blood samples were taken every 15 min from –15 min up to 90 min. GH deficiency was diagnosed when the GH peak after ARG + GHRH was less than 9 μg/liter, according to previous studies (24, 25). Pituitary ACTH deficiency was diagnosed when serum 0800 h cortisol levels were low (<3.6 μg/dl; 100 nmol/liter) or cortisol peaked at less than 21 μg/dl (600 nmol/liter) in response to synthetic ACTH stimulation (250 μg, iv) together with an increase from basal of less than 8 μg/dl (220 nmol/liter), whereas TSH deficiency was diagnosed when a subnormal serum free T_4 level (<9 pmol/liter) was associated with a low or normal TSH level (0.3–5 mU/liter). Serum IGF-I, testosterone and free thyroid hormones, serum and urinary Na^+ and K^+ measurements were assessed every 6 months for the adequacy of hormone replacement therapy. To evaluate the recovery of pituitary function, withdrawal from replacement therapy was performed after 6 and 12 months of cabergoline therapy.

Treatment protocol

For all patients, cabergoline was the first line therapy. According to a previous study (12), treatment was started orally at a dose of 0.5 mg once weekly for the first week, then twice weekly. Dose adjustment was carried out every 2 months on the basis of PRL suppression; the dose was increased when hormone levels were more than 15 μg/liter. In large macroprolactinomas showing an infrasellar extension, the starting dose of cabergoline was 0.25 mg once a week for the first week, then twice weekly to reduce the dosage below levels associated with risk of rhinorrhea (25). Dose adjustment was performed as above. In patients not normalizing PRL levels, the dose was progressively increased to 3.5 mg/wk. All patients were followed for 24 months.

Imaging studies

Tumor mass was evaluated by MRI as previously reported (2, 22, 27). MRI studies were performed on clinical 0.5 T and 1T scanners, using T1 weighted-gradient recalled-echo (repetition time, 200–300 msec; echo time, 10–12 msec; flip angle, 90°; four signal averages) in the sagittal and coronal planes. The acquisitions were repeated before and after the administration of 0.1 mmol of gadolinium chelate. MRI was performed before and after 3 and 6 months of treatment in patients with macro- and before and after 6 months of treatment in those with microprolactinoma. All tumor diameters were measured, and the maximal tumor diameter (expressed in millimeters) was considered in all adenomas for further analysis. Based on the criticism that tumors are seldom of spherical shape and thus the calculation of tumor volume according to the ellipsoid formula could lead to misleading results, in disagreement with a previous study (22) and in agreement with more recent studies (1, 2, 28), we evaluated tumor shrinkage as reduction of the maximal tumor diameter compared with baseline by a semiquantitative four-point scale as follows: less than 10% as absent, 10–20% as mild, 20–30% as moderate, and as more than 30% as remarkable.

TABLE 1. Demographic, endocrine, and radiological findings in patients and controls at study entry

	Macroprolactinomas	Controls	*P*	Microprolactinomas	Controls	*P*
No. of subjects	41	41		10	10	
Age (yr)	32.7 ± 13.6	32.7 ± 13.6	0.9	33.5 ± 12.5	33.6 ± 12.5	1.0
Serum PRL (μg/liter)	2019 ± 2123	6.6 ± 2.5	<0.0001	182.0 ± 62.8	5.7 ± 2.2	<0.0001
Serum FSH (IU/liter)	3.8 ± 0.5	4.8 ± 0.5	<0.0001	4.1 ± 0.7	4.4 ± 0.6	<0.0001
Serum LH (IU/liter)	3.1 ± 0.8	5.1 ± 0.7	<0.0001	3.5 ± 0.5	5.6 ± 0.7	<0.0001
Serum testosterone (μg/liter)	2.5 ± 0.8	4.6 ± 0.6	<0.0001	2.8 ± 0.6	4.8 ± 0.6	<0.0001
Maximal tumor diameter (mm)	23.1 ± 10.8			8.1 ± 1.6		
No. of patients with hypopituitarism (%)	22 (53.6)			0/0		
No. of patients with visual field defects (%)	17 (41.4)			0/0		
No. of patients with headache (%)	14 (34.1)			2 (20)		
No. of patients with galactorrhea (%)	8 (19.5)			0/0		
Seminal volume (ml)	2.0 ± 0.9	4.3 ± 0.6	<0.0001	2.6 ± 0.9	4.2 ± 0.6	0.026
pH	7.8 ± 0.2	7.6 ± 0.3	0.48	7.7 ± 0.2	7.6 ± 0.5	0.48
Sperm count (10^6/ml)	31.3 ± 22.6	52.4 ± 6.3	<0.0001	27.1 ± 19.2	45.9 ± 8.9	0.064
Total sperm count (10^6/vol)	88.6 ± 90.9	226.6 ± 51.8	<0.0001	66.5 ± 70.4	192.1 ± 40.6	0.026
Sperm total motility (%)	26.8 ± 12.5	58.1 ± 8.3	<0.0001	21.3 ± 11.8	62.5 ± 7.5	0.002
Forward progression (%)	14.4 ± 7.9	32.7 ± 6.7	<0.0001	13.8 ± 7.9	36.5 ± 7.1	0.004

Data are shown as mean ± SD. Normal ranges are as follows: FSH and LH, 3–8 IU/liter; testosterone, 3–9 μg/liter; and PRL, 5–15 μg/liter. For seminal fluid analysis, volume > 2 ml; pH = 7.2–8.0; sperm concentration > 20×10^6 spermatozoa/ml; total sperm count > 40×10^6 spermatozoa per ejaculate; and total motility ≥50% or ≥25% forward progression within 60 min of ejaculation.

Visual perimetry

In patients with macroprolactinoma, the assessment of visual field defects, by Goldmann-Friedmann perimetry, and visual acuity was performed at baseline. The ophthalmological examination was repeated after 3, 6, 12, 18, and 24 months of treatment in the 11 patients with quadrantopia or hemianopia and every week for the first month and then every month in the six patients showing more severe visual field defects.

Semen analysis

The semen analysis was performed after 3 d of sexual abstinence, according to World Health Organization guidelines (29). The evaluation of number and motility of the spermatozoa was performed in a Makler counting chamber (40×). Sperm morphology was analyzed after dilution (1:1) with saline phosphate buffer and Giemsa. Normal ranges of sperm patterns (29) are as follows: volume more than 2 ml, pH 7.2–8.0, sperm concentration more than 20×10^6 spermatozoa/ml, total sperm count more than 40×10^6 spermatozoa per ejaculate, and total motility at least 50% or at least 25% forward progression within 60 min of ejaculation.

Assays

Serum FSH, LH, and PRL levels were assessed by RIA using commercial kits. Testosterone levels were assessed using Immulite solid-phase chemiluminescent enzyme immunoassay commercial kits. Serum PRL levels were assessed by RIA using commercial kits. The intra- and interassay coefficients of variation (CVs) were 5 and 7%, respectively. Normal ranges in our laboratory were as follows: FSH and LH, 3–8 IU/liter; testosterone, 3–9 μg/liter; and PRL, 5–15 μg/liter. Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits. The sensitivity of the assay was 0.2 μg/liter. The intra- and interassay CVs were 4.5 and 7.9%, respectively. Serum IGF-I was measured by RIA after ethanol extraction. The normal range in men aged 20–30, 31–40, 41–50, and more than 60 yr is 118–513, 112–493, 100–316, and 78–258 μg/liter, respectively. The sensitivity of the assay is 0.8 μg/liter. The intraassay CVs were 3.4, 3.0, and 1.5% for the low, medium, and high points of the standard curve, respectively. The interassay CVs were 8.2, 1.5, and 3.7% for the low, medium, and high points of the standard curve. Serum TSH levels were measured using an IRMA (Delfia, Wallac, Inc., Turku, Finland) that has a detection limit of 0.03 mU/liter. Serum concentrations of free T_3 and T_4 were determined by RIA Lisophase kit (Technogenetics, Milan, Italy). Plasma ACTH concentrations were measured by IRMA using commercial kits. The normal ACTH range was 10–130 ng/liter at 0800 h and 10–80 ng/liter at 2000 h. Serum cortisol concentrations were measured by RIA using commercial kits. The normal range was 50–200 μg/liter at 0800 h and 50–90 μg/liter at 2000 h.

Statistical analysis

Data are reported as mean ± SD unless otherwise specified. The statistical analysis was performed by the SPSS Inc. (Chicago, IL) package using the ANOVA for repeated measures to evaluate the effect of cabergoline throughout the follow-up in the patients' group, the Mann-Whitney test to compare responsive *vs.* resistant patients and macro- *vs.* microprolactinomas, and the Student's *t* test for paired data to compare patients *vs.* controls. Statistical significance was set at 5%. Correlations were performed by calculating the Pearson's or Spearman's coefficient according to data normally or not normally distributed.

Results

Patients' profile at study entry

At baseline, PRL levels were significantly higher in macro- than in microprolactinomas, as expected (Table 1). Among patients with macroprolactinoma, 17 (41.4%) had visual field defects, 14 (34.1%) had headache, and eight (19.5%) had galactorrhea, whereas among those with microprolactinoma, none had visual field defects or galactorrhea and two had headache (20%). Hypopituitarism, apart from hypogonadism, was present in none with micro and in 22 with macroprolactinoma (53.6%); 16 patients had GH deficiency (39%), 10 had TSH deficiency (24.4%), and five had ACTH deficiency (12.2%). Testosterone deficiency was present in 30 patients with macro- (73.2%) and in five with microprolactinoma (50%; $P = 0.3$). Eight patients with macro- (19.5%) and two with microprolactinoma (20%) were referred to the endocrinologist for infertility. FSH, LH, and testosterone levels and semen morphology, all impaired compared with controls (Table 1), were similar in patients with macro- and microprolactinoma. In detail, in patients with macro- or microprolactinoma, respectively, seminal volume was less than 2 ml in 17 (41.5%) and 4 (40%), total sperm count was less than 40×10^6 spermatozoa per ejaculate in 17 (41.5%) and 5 (50%), total motility was less than 50% in all, and forward progression was <25% in 37 (90%); and 9 (90%). PRL levels correlated with the maximal tumor diameter ($r = 0.94$; $P < 0.0001$), testosterone levels ($r = -0.43$; $P = 0.001$), and cabergoline dose ($r = 0.53$; $P < 0.0001$), but with none of the sperm parameters.

Effect of 24 months of treatment on the normalization of PRL levels

During cabergoline treatment, PRL levels (Fig. 1) lowered progressively in both groups. At the 24-month follow-up, PRL levels were normalized in 31 patients with macro- (75.6%) and in eight with microprolactinoma (80%, $P = 0.9$); galactorrhea disappeared in all patients. The dose required to normalize PRL levels was 1 mg/wk in 17 patients with macro- (41.2%) and in all with microprolactinoma and 1.5 mg/wk in eight (19.5%) and 2 mg/wk in seven (17%) patients with macroprolactinoma. In two patients with macro- and five with microprolactinoma, the dose was reduced to 0.5 mg/wk. In the 10 patients with macro- and two with microprolactinoma not achieving PRL normalization and classified as resistant to cabergoline, the dose was increased up to 7 mg/wk without any significant PRL-lowering effect, and thus the dose was lowered to 3.5 mg/wk during the rest of the follow-up. The comparison between patients resistant and responsive to cabergoline therapy is shown in Table 2. Basal PRL levels were higher in resistant patients with macro- but not with microprolactinoma (Table 2).

Effect of 24 months of treatment on tumor shrinkage

Maximal tumor diameter progressively reduced during treatment (Fig. 1), up to by 73.7 ± 22.6% in macro- and by 72.8 ± 28.3% in microprolactinoma ($P = 0.91$) at the 24th month follow-up. A remarkable shrinkage (>30% decrease of the maximal tumor diameter) was found in all macroprolactinomas and in all but one microprolactinomas; 15 macro- (30%) and seven microprolactinomas (46.7%, $P = 0.37$) disappeared after 24 months of treatment. None of the patients had evidence of any increase in tumor size during therapy, neither in those resistant to the treatment. Individual results, according with therapy responsiveness are shown in Fig. 2. Visual field defects disappeared in 15 (75%) patients with macro- and headache disappeared in 15 (83%) with macro- and in one with microprolactinoma (50%). The percent PRL decrease was weakly correlated with the percent decrease of the maximal tumor diameter ($r = 0.38$; $P = 0.005$). The maximal tumor diameter before therapy

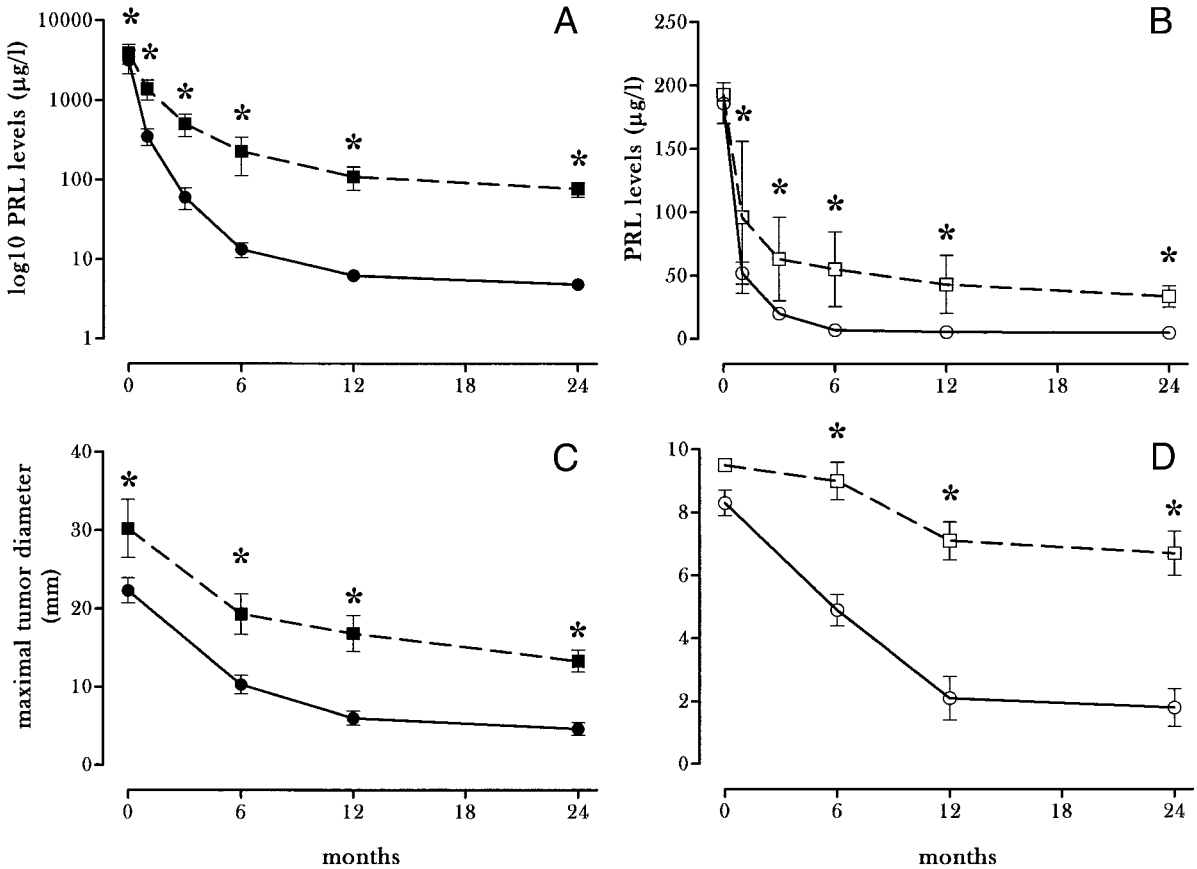

FIG. 1. Profile of PRL levels (*top*) and tumor size (*bottom*) during cabergoline therapy in patients with macroprolactinomas (A, C) and microprolactinomas (B, D). Data are shown as mean ± SEM according to the response to the therapy. ●, Solid line indicates responsive macroprolactinomas (n = 39); ○, solid line indicates responsive microprolactinomas (n = 13); ■, dashed line indicates resistant macroprolactinomas (n = 11); □, dashed line indicates resistant micorprolactinomas (n = 2). *, $P < 0.01$ *vs.* responsive patients.

TABLE 2. Response to cabergoline treatment at the 24-month follow-up in men with macro- and microprolactinomas

	Macroprolactinomas		*P*	Microprolactinomas		*P*
	Responsive	Resistant		Responsive	Resistant	
No. of subjects	31	10		8	2	
Age (yr)	34.7 ± 14.8	26.2 ± 5.2	0.87	34.0 ± 13.9	31.5 ± 6.4	0.6
Basal PRL levels (μg/liter)	1208 ± 2227	2672 ± 1696	0.049	171.0 ± 34.2	226.0 ± 42.4	0.93
PRL levels after 2-yr cabergoline (μg/liter)	4.6 ± 3.3	55.6 ± 39.2	<0.0001	4.8 ± 2.5	29.5 ± 17.7	0.03
% PRL decrease	99.1 ± 0.9	96.8 ± 3.2	0.0002	97.2 ± 1.6	75.2 ± 27.6	0.03
Basal testosterone levels (μg/liter)	2.6 ± 0.9	2.0 ± 0.6	0.12	2.9 ± 0.6	2.3 ± 0.2	0.93
Testosterone levels after 2-yr cabergoline (μg/liter)[a]	4.8 ± 0.4	–	0.04	5.0 ± 0.6	4.9	–
Basal maximal tumor diameter (mm)	20.6 ± 9.8	30.6 ± 10.7	0.019	8.0 ± 1.8	8.6 ± 1.4	0.1
Maximal tumor diameter after 2-yr cabergoline (mm)	3.6 ± 3.9	15.4 ± 7.6	<0.0001	1.6 ± 2.2	5.6 ± 2.5	0.03
% Decrease of maximal tumor diameter	84.4 ± 16.3	52.0 ± 13.7	<0.0001	81.6 ± 25.7	36.4 ± 19.2	0.03
Maximal cabergoline dose (mg/wk)	1.4 ± 0.4	3.2 ± 0.5	<0.0001	1.0 ± 0.2	2.7 ± 1.1	0.03

[a] These values refer only to patients not requiring testosterone replacement. Number of patients in each column are respectively 25, 0, 5 and 1.

was higher in resistant patients with macro- but not with microprolactinoma (Table 2).

Effect of 24 months treatment on the residual pituitary function

According to our study protocol, the ARG + GHRH test was performed 6 months after cabergoline treatment began. GH deficiency was diagnosed in 12 patients with macroprolactinoma (29.3%), six of the 16 showing low IGF-I levels before therapy and six newly diagnosed; all 12 received GH replacement. In none of these 12 patients did the tumor regrow during GH replacement, but it continued to decrease, as in the cases not receiving GH replacement. Another seven patients of the 16 showing low IGF-I levels before therapy had a GH peak between 9 and 16.5 μg/liter and were classified as partial GH deficient, but IGF-I levels returned to the normal range for age and sex. When these seven patients were retested after 12 months of cabergoline therapy, the GH

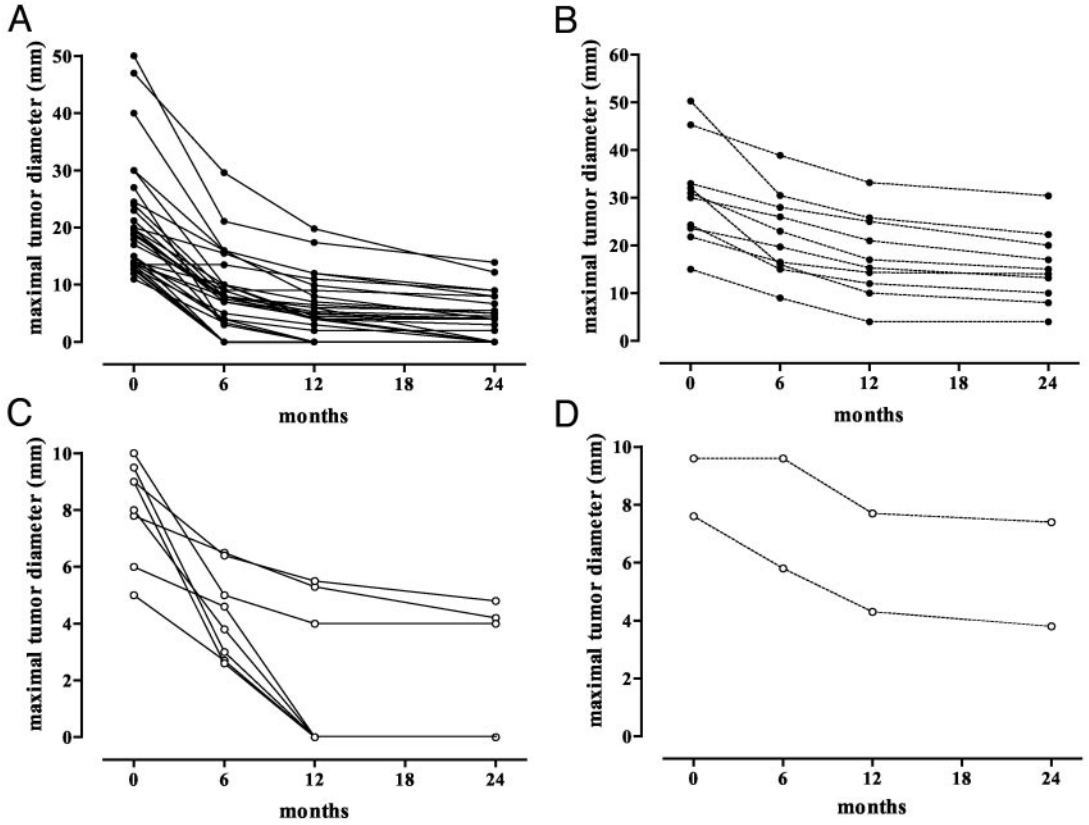

FIG. 2. Individual results of the maximal tumor diameter before and during treatment in 31 patients with macroprolactinoma responsive to cabergoline (A), in 10 patients with macroprolactinoma resistant to cabergoline (B), in eight patients with microprolactinoma responsive to cabergoline (C), and in two patients with microprolactinoma resistant to cabergoline (D). ●, Macroprolactinomas; ○, microprolactinomas; *solid line*, responsive patients; *dashed line*, resistant patients.

peak to the ARG + GHRH test was above 16.5 μg/liter in five and was still between 9 and 16.5 μg/liter in the remaining two patients. In the hypopituitary patients with macroprolactinoma, replacement therapy remained unchanged during treatment except for three who withdrew from cortisone replacement after confirmation of normal ACTH reserve by ACTH test. So, GH secretion was recovered in 62.5% and ACTH secretion in 60% of cases. After 6 months of treatment, testosterone levels were normalized in 25 patients with macro- (60.9%) and in six with microprolactinomas (60%); the remaining 20 patients (16 with macro- and four with microprolactinoma) required testosterone replacement (in 14) or gonadotropin replacement (in six). This latter treatment was followed by pregnancy for four of the six patients within 12 months from beginning treatment. At the end of the 24-month follow-up, libido disturbances improved in 24 macro- (58.5%) and in nine microprolactinomas (90%).

Effect of 24 months of cabergoline treatment on seminal fluid

The 20 patients showing persistently low testosterone levels and requiring androgen or gonadotropin replacement were excluded from this analysis, which is based on data obtained in 31 patients. All these 31 patients achieved PRL normalization except one with a microprolactinoma who had a near normal PRL level (17–20 μg/liter). Because there were no significant differences in the semen results between patients with macro- and microprolactinoma at study entry, the effect of cabergoline treatment on semen fluid was analyzed considering the two groups together. As shown in Table 3, a significant improvement of semen parameters was observed during the follow-up. After 6 and 12 months of therapy, despite the normalization of testosterone levels, seminal parameters remained impaired compared with controls, whereas after 24 months of therapy all seminal parameters were similar to controls. However, seminal fluid and sperm count were normalized in all patients within the first year of therapy, and motility remained only slightly impaired in a few patients (Table 4).

Tolerability to cabergoline treatment

Side effects were very mild and infrequent. Only three patients had side effects, that most commonly being nausea and drowsiness. One was an elderly patient who could not increase the dose up to 1 mg/wk, and two others had side effects after the dose of 3 mg/wk. No patient was withdrawn from treatment because of side effects.

Discussion

This 24-month prospective study of cabergoline outcome in men with prolactinoma shows that 1) PRL was normalized

TABLE 3. Seminal fluid analysis during 2-yr cabergoline treatment in the 31 patients with prolactinoma (25 with macro- and six with microadenoma) achieving normal testosterone levels after 6 months of treatment*

	Baseline	6 months	12 months	24 months	P^a	Controls	P^b
PRL levels (μg/liter)	853.2 ± 958.2	6.8 ± 5.4	5.0 ± 4.2	4.7 ± 3.8	<0.0001	6.5 ± 2.3	0.009
Testosterone levels (μg/liter)	2.8 ± 0.8	4.3 ± 0.6	4.8 ± 0.4	4.9 ± 0.4	<0.0001	4.7 ± 0.5	0.09
Seminal volume (ml)	2.3 ± 0.9	3.2 ± 0.8[c]	3.5 ± 0.7[c]	4.3 ± 0.6	<0.0001	4.2 ± 0.6	0.46
Sperm count (10^6/ml)	25.3 ± 13.8	34.6 ± 13.0[c]	45.5 ± 10.9[c]	51.2 ± 8.5	<0.0001	54.7 ± 9.9	0.1
Total sperm count (10^6/vol)	61.4 ± 51.6	114.7 ± 61.7[c]	155.4 ± 59.7[c]	220.1 ± 52.5	<0.0001	233.0 ± 51.2	0.27
Sperm total motility (%)	24.7 ± 12.7	39.1 ± 10.8[c]	50.9 ± 9.8[c]	58.2 ± 8.1	<0.0001	57.6 ± 8.2	1
Forward progression (%)	14.5 ± 6.8	18.5 ± 7.9[c]	28.2 ± 6.6[c]	32.2 ± 6.0	<0.0001	32.4 ± 6.4	1

*All but one patient, who had near-normal levels of 17–20 μg/liter, also achieved normal PRL levels. Comparison was made to the whole group of 51 controls. Data are shown as mean ± SD.

[a] P values refer to the ANOVA for repeated measures in the patient group.

[b] P values refer to the Student's t test for unpaired data between patients' data after 24 months and controls.

[c] $P < 0.01$ *vs.* controls.

TABLE 4. Prevalence (%) of semen abnormalities in the 26 men with macroprolactinoma and in the six with microprolactinoma, who achieved PRL and testosterone normalization, before and after 24 months of cabergoline therapy

	Macroprolactinomas (months)				Microprolactinomas (months)			
	0	6	12	24	0	6	12	24
Seminal volume (ml)	30.7	0	0	0	16.7	0	0	0
Sperm count (10^6/ml)	42.3	11.5	0	0	50	33.3	0	0
Total sperm count (10^6/vol)	50	7.7	0	0	50	0	0	0
Sperm total motility (%)	100	76.9	50	11.5	100	83.3	16.7	16.7
Forward progression (%)	96.1	76.9	50	3.8	83.3	66.6	16.7	16.7

in 39 patients (76.5%) without any difference between those with macro- (75.6%) or microprolactinoma (80%); 2) all patients but one with a resistant microprolactinoma achieved remarkable tumor shrinkage, in line with previous findings obtained in a mixed cohort of women and men with prolactinoma (2); 3) more than 60% of the patients recovered testosterone (60.8%), GH (62.5%), and ACTH (60%) deficiency during treatment; and 4) sperm volume and number were normalized in all patients, achieving normal testosterone levels during the first 12 months, whereas motility normalized in more than 80% of cases after 24 months of therapy. These data rule out the hypothesis, based on studies in tumor cells (6, 7), that men bear more aggressive tumors less likely to be responsive to pharmacotherapy than women, because the outcome of cabergoline treatment in the current study did not differ from that reported in other studies with similar treatment duration (2–4, 6, 18, 24–27).

Our data are of clinical relevance because results of treatment outcome in general, and of pharmacotherapy in particular, in men with hyperprolactinemia are scant compared with women. This is due to the fact that PRL excess is more frequent in women than in men (1). Additionally, results have usually been analyzed in small retrospective studies (7–17) with only one exception (1). In our preliminary study aimed at investigating the role of gender in clinical presentation and response to cabergoline (1), we analyzed the results of a short-term treatment in a larger series of patients including the current one. However, we did not observe any difference in treatment outcome between men and women, even when the prevalence of microprolactinomas was much higher in women than in men, and the increased prevalence of small lesions in women was likely to be the determinant of the higher success rate of PRL normalization in the entire series of women (1). In the largest series reported so far by Verhelst *et al.* (18), 102 men were shown to have a significantly lower likelihood of achieving normoprolactinemia than women (75 *vs.* 90%). However, the most likely explanation, self-acknowledged by the authors, was that men also presented more frequently a macroprolactinoma than women (86 *vs.* 38%). In contrast, in our rather large series of 51 men studied prospectively, although confirming the evidence that the majority presented with a macroadenoma (80.4%), the outcome in terms of PRL normalization was similar. Normalization of PRL levels was accompanied by normalization of testosterone secretion in 60.8% of cases, GH in 62.5%, and ACTH deficiency in 60%. The recovery of pituitary function after cabergoline treatment has never been investigated in detail. GH deficiency was reported to be reversed by cabergoline treatment in a very small cohort of patients studied prospectively (30), but in our series, GH replacement was required in 12 cases, 50% of them presenting this GH deficiency at study entry. It should be noted that at study entry the diagnosis of GH deficiency was based only on IGF-I levels and not on the GH peak after the ARG + GHRH test to avoid any effect of this stimulating test on an untreated macroprolactinoma. This different approach to the diagnosis of GH deficiency could have underestimated the prevalence of this alteration at study entry and hence its recovery after therapy. Moreover, a slightly reduced GH response to ARG + GHRH not fulfilling the criteria for GH replacement (31) was observed in another seven patients (13.7%) after 6 months of therapy. The GH response was normalized at the 12-month follow-up in five of seven cases and remained slightly abnormal in a minority (two of seven) throughout the study. Importantly, in none of GH-replaced patients did tumor regrow, but it continuously shrank without any apparent difference compared with those not requiring GH replacement. Notably, 60% of the patients who were receiving cortisol replacement at study entry could be withdrawn from therapy within the first year of cabergoline

treatment. This suggests that 6-monthly withdrawal from replacement therapies could be indicated in patients with macroprolactinoma undergoing cabergoline treatment at least during the first years of treatment.

Compared with women, men have more frequently macroprolactinomas (1, 18) with a more aggressive growth profile (6, 7). Gender-related factors modifying the rate of tumor growth and inducing a lower effectiveness of pharmacotherapy were thus hypothesized in men. This hypothesis was supported by the results of a large retrospective study (18). The results of our current prospective study demonstrated that PRL levels were normalized in 76% of patients with macro- and 80% of those with microprolactinoma and that all tumors but one were remarkably reduced in size. As expected, the tumor-shrinking effect of cabergoline was greater in responsive than in resistant patients, but interestingly, reduction of tumor size was evident also in the latter group, reinforcing our previous findings (2). These figures are not different from those observed in a cohort of women, including 49 with macro- and 81 with microprolactinoma treated throughout a similar period of time; remarkable tumor shrinkage was found in 81.6% of macro- ($P = 0.6$) and in 93.8% of microprolactinomas ($P = 0.35$) (our unpublished data). On the other hand, we recently reported that the amount of tumor shrinkage, evaluated as nadir maximal tumor diameter during cabergoline treatment, predicted the recurrence of hyperprolactinemia without any gender difference (28). Additionally, most patients (76.4%) also obtained improvement of visual field defects, and only minor visual defects were evident at the end of the 24-month treatment period.

This study also confirms previous findings obtained in smaller cohorts of patients followed for shorter periods of time (19, 20), that prolonged normalization of PRL levels by cabergoline has beneficial effects on seminal volume, sperm count, and motility. Increase of sperm count and improvement of sperm motility was, however, observed only in a subset of patients obtaining normalized PRL levels during treatment, as these were the only patients who achieved testosterone normalization. A short-term treatment was unable to completely restore sperm motility, whereas seminal volume and sperm count were normalized earlier. Hyperprolactinemia causes a spermiogenic arrest and induces an impairment of sperm motility with cytological findings similar to that observed in the prepubertal testis (32, 33). The evidence that sperm motility improved later than sperm count is in accordance with the hypothesis of a maturational spermatogenic arrest in analogy with the prepubertal stage in the rat.

Finally, the dose of cabergoline used in this study is in line with that reported in the literature, slightly higher in macro- than in microadenomas, as expected because they were found to be directly correlated with PRL levels (present study and Ref. 2). It should be noted that based on a previous experience (2) the dose of cabergoline was not increased over 3.5 mg/wk, except in a few cases for a short period of treatment, because additional dose increments were shown not to improve PRL suppression. However, PRL levels were reduced by 96.8 ± 3.2% in resistant patients with macro- and by 75.2 ± 27.6% in those with microprolactinoma, indicating that all cases included in the current series were sensitive to cabergoline, even if displaying different degrees of sensitivity.

In conclusion, cabergoline treatment for 24 months at a median dose of 1.5 mg/wk in patients with macro- and 1 mg/wk in those with microprolactinomas induced normalization of PRL levels in the majority of men, restoring testosterone, GH, and ACTH secretion in approximately 60% of cases, normalizing sperm volume and count, improving sperm motility, and inducing remarkable tumor shrinkage, even in those not achieving PRL normalization, and so recovering symptoms due to tumor compression on other critical structures. Cabergoline therapy was well tolerated, and only 4.5% of patients complained of side effects at the highest doses. These data demonstrate that cabergoline treatment is as effective and safe in men as in women with prolactinoma and can be successfully used as primary therapy even in men bearing large macroprolactinomas. Reevaluation of pituitary function is advised biannually, at least during the first year of therapy, because of the high degree of recovery of hypopituitarism during cabergoline treatment. Finally, no increase of tumor size was observed in the patients with microprolactinoma undergoing GH replacement during treatment, indicating that GH replacement is safe even in patients still bearing detectable prolactinomas.

Acknowledgments

We thank Angelo Di Francia for his excellent technical support.

Received June 5, 2003. Accepted January 13, 2004.

Address all correspondence and requests for reprints to: Annamaria Colao, M.D., Ph.D., Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, via S. Pansini 5, 80131 Naples, Italy. E-mail: colao@unina.it.

This study was partially supported by a grant of the Italian Minister of Research and University in Rome (no. 2003068735).

References

1. **Colao A, Di Sarno A, Cappabianca P, Briganti F, Pivonello R, Di Somma C, Faggiano A, Biondi B, Lombardi G** 2003 Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. Eur J Endocrinol 148:325–331
2. **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 to bromocriptine in hyperprolactinemia: prevalence, clinical definition and therapeutic strategy. J Clin Endocrinol Metab 86:5256–5261
3. **Colao A, Di Sarno A, Sarnacchiaro F, Ferone D, Di Renzo GF, 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
4. **Biller BMK, Molitch ME, Vance ML, Cannistraro KB, Davis KR, Simons JA, Schoenfelder JR, Klibanski A** 1996 Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J Clin Endocrinol Metab 81:2338–2343
5. **Colao A, Loche S, Cappa M, Di Sarno A, Landi ML, Sarnacchiaro F, Facciolli G, Lombardi G** 1998 Prolactinomas in children and adolescents: clinical presentation and long-term follow-up. J Clin Endocrinol Metab 83:2777–2780
6. **Cannavò S, Curtò L, Squadrito S, Almoto B, Vieni A, Trimarchi F** 1999 A first choice treatment in patients with previously untreated prolactin-secreting pituitary adenoma. J Endocrinol Invest 22:354–359
7. **Calle-Rodrigue RD, Giannini C, Scheithauer BW, Lloyd RV, Wollan PC, Kovacs KT, Stefaneanu L, Ebright AB, Abboud CF, Davis DH** 1998 Prolactinomas in male and female patients: a comparative clinico-pathology study. Mayo Clin Proc 73:1046–1052
8. **Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J** 1997 Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. J Clin Endocrinol Metab 82:2102–2107
9. **Somma M, Beauregard H, Rasio E** 1981 Le prolactinome chez l'homme: evaluation préopératoire de 40 patients. Neurochirurgie 27:37–39

10. **Eversmann T, Eichinger R, Fahlbusch R, Rjosk HK, von Werder K** 1981 Die hyperprolaktinämie beim mann: klinik und therapie. Schw Med Wochensch 111:1782–1789
11. **Spark RF, Wills CA, O'Reilly G, Ransil BJ, Bergland R** 1982 Hyperprolactinaemia in males with and without pituitary macroadenomas. Lancet 2:129–132
12. **Hulting AL, Muhr C, Lundberg PO, Werner S** 1985 Prolactinomas in men: clinical characteristics and the effect of bromocriptine treatment. Acta Medica Scandinava 217:101–109
13. **Walsh JP, Pullan PT** 1997 Hyperprolactinaemia in males: a heterogeneous disorder. Aust N Z J Med 27:385–390
14. **Grisoli F, Vincentelli F, Jaquet P, Guibout M, Hassoun J, Farnarier P** 1980 Prolactin secreting adenoma in 22 men. Surg Neurol 13:241–247
15. **Berezin M, Shimon I, Hadani M** 1995 Prolactinoma in 53 men: clinical characteristics and modes of treatment (male prolactinoma). J Endocrinol Invest 18:436–441
16. **Di Somma C, Colao A, Di Sarno A, Klain M, Landi ML, Facciolli G, Pivonello R, Panza N, Salvatore M, Lombardi G** 1998 Bone density and bone marker responses to dopamine agonist therapy in hyperprolactinemia males. J Clin Endocrinol Metab 83:807–813
17. **Pinzone JJ, Katznelson L, Danila DC, Pauler DK, Miller CS, Klibanski A** 2000 Primary medical therapy of micro- and macroprolactinomas in men. J Clin Endocrinol Metab 85:3053–3057
18. **Verhelst J, Abs R, Maiter D, 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
19. **Colao A, De Rosa M, Sarnacchiaro F, Di Sarno A, Landi ML, Iervolino E, Zarrilli S, Merola B, Lombardi G** 1996 Chronic treatment with CV 205-52 restores the gonadal function in hyperprolactinemic males. Eur J Endocrinol 135:548–552
20. **De Rosa M, Colao A, Di Sarno A, Ferone D, Landi ML, Zarrilli S, Paesano L, Merola B, Lombardi G** 1998 Cabergoline treatment rapidly improves gonadal function in hyperprolactinemic males: a comparison with bromocriptine. Eur J Endocrinol 138:286–293
21. **De Rosa M, Zarrilli S, Vitale G, Di Somma C, Orio F, Tauchmanova' L, Lombardi G, Colao A** 2004 Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. J Clin Endocrinol Metab 89:621–625
22. **Colao A, Di Sarno A, Landi ML, Scavuzzo F, Cappabianca P, Pivonello R, Volpe R, Di Salle F, Cirillo S, Annunziato L, Lombardi G** 2000 Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. J Clin Endocrinol Metab 85:2247–2252
23. **Ghigo E, Aimaretti G, Gianotti L, Bellone J, Arvat E, Camanni F** 1996 New approach to the diagnosis of growth hormone deficiency in adults. Eur J Endocrinol 134:352–356
24. **Colao A, Di Somma C, Pivonello R, Loche S, Aimaretti G, Cerbone G, Faggiano A, Corneli G, Ghigo E, Lombardi G** 1999 Bone loss is correlated to the severity of growth hormone (GH) deficiency in adult patients with hypopituitarism. J Clin Endocrinol Metab 84:1919–1924
25. **Colao A, Cerbone G, Pivonello R, Aimaretti G, Loche S, Di Somma C, Faggiano A, Corneli G, Ghigo E, Lombardi G** 1999 The growth hormone (GH) response to arginine plus GH releasing hormone test is correlated to the severity of lipid profile abnormalities in adult patients with GH deficiency. J Clin Endocrinol Metab 84:1277–1282
26. **Cappabianca P, Lodrini S, Felisati G, Peca C, Cozzi R, Di Sarno A, Cavallo LM, Giombini S, Colao A** 2001 Cabergoline-induced CSF rhinorrhea in patients with macroprolactinoma: report of three cases. J Endocrinol Invest 24:183–187
27. **Colao A, Di Sarno A, Landi ML, Cirillo S, Sarnacchiaro F, Facciolli 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
28. **Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G** 2003 Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med 349:2023–2033
29. **World Health Organization** 1999 Laboratory manual for the examination of human semen and semen-cervical mucus interaction. Cambridge, UK: Cambridge University Press
30. **George LD, Nicolau N, Scanlon MF, Davies JS** 2000 Recovery of growth hormone secretion following cabergoline treatment of macroprolactinomas. Clin Endocrinol (Oxf) 53:595–599
31. **Growth Hormone Research Society (GRS)** 1998 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on adult growth hormone deficiency. J Clin Endocrinol Metab 83:379–381
32. **Bartke A** 1985 Male hamster endocrinology. In: Siegel HI, ed. The hamster: reproduction and behaviour. New York: Plenum Press; 73–98
33. **Segal S, Yaffe H, Laufer N, Ben-David M** 1979 Male hyperprolactinemia: effect on fertility. Fertil Steril 32:556–561

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.