

## RESEARCH

# Management of prolactinoma: a survey of endocrinologists in China

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## Abstract

**Objective:** To assess the current management of prolactinoma among endocrinologists in China.

**Methods:** An online survey of a large sample of endocrinologists was conducted in China. The questionnaire included 21 questions related to controversial issues about the management of prolactinomas. Doctors in the endocrinology department of a university-affiliated hospital or a comprehensive secondary hospital in 12 cities from East, West, South, North and Middle China were surveyed.

**Results:** A total of 290 valid questionnaires were collected, and the response rate was 40%. When hyperprolactinemia occurred, 97% of the respondents would test thyroid-stimulating hormone routinely. 22% of the respondents considered that prolactin levels <100 ng/mL exclude the presence of a prolactinoma. Only 9% of the respondents believed that prolactin >250 ng/mL could occur in all the following situations as macroprolactinoma, microprolactinoma, macroprolactinemia and drug-induced hyperprolactinemia. Surgery was not recommended by 272 (94%) endocrinologists as the first choice for treating microprolactinomas. 58% and 92% of endocrinologists would start drug treatment for microprolactinomas and macroprolactinomas at diagnosis. 70% and 40% chose to withdraw treatment after 2–3 years of prolactin normalization in microprolactinomas and macroprolactinomas. In case of pregnancy, 57% of the respondents considered bromocriptine as choice for women patients. Drug discontinuation after pregnancy was advocated in 63% and 27% for microprolactinoma and macroprolactinoma. Moreover, 44% of endocrinologists believed that breastfeeding was allowable in both micro- and macroprolactinoma.

**Conclusion:** This is the first study to investigate the management of prolactinomas among endocrinologists in China. We found that the current clinical treatment was not uniform. Therefore, it is necessary to strengthen the training of endocrinologists to improve clinical diagnosis and treatment practices.

### Key Words

- ▶ prolactinoma
- ▶ endocrinologist
- ▶ survey

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## Introduction

Prolactinoma is the most common functional pituitary tumor, accounting for approximately 40–60% of functional pituitary tumors (1). Microadenomas are defined as tumors with a diameter of <1 cm and macroadenomas as having a diameter of ≥1 cm (2). Clinical manifestations include hyperprolactinemia and local tumor mass effects.

The former can cause amenorrhea, lactation and infertility in females. In males, sexual dysfunction and infertility are the most common deleterious effects. Tumor mass effects can cause visual field defects, decreased vision, headaches and can even be life threatening. Drug therapy is recommended for prolactinoma, and the dopamine

receptor agonists (DAs) bromocriptine and cabergoline are commonly prescribed (3).

However, in the current clinical practice, there are still controversies concerning appropriate diagnosis and treatment of prolactinoma, such as the identification of hyperprolactinemia, the choice of treatment methods, the duration of drug treatment and management of pregnancy and breastfeeding. In recent years, two studies have conducted questionnaire surveys of clinicians' management of prolactinomas reflecting self-reported clinical diagnoses and treatment (4, 5). However, no similar data are available from China. Therefore, we conducted a questionnaire survey to document the management of prolactinoma by Chinese endocrinologists.

## Materials and methods

### Questionnaire design

With reference to the Brazilian questionnaire (Supplementary data, see section on [supplementary data](#) given at the end of this article) on the clinical response to prolactinoma, we translated and designed a Chinese version. A total of 21 questions were provided, including the diagnosis, treatment and management in pregnancy and breastfeeding of prolactinoma.

### Questionnaire survey

Doctors in the endocrinology department of university-affiliated hospitals or comprehensive secondary hospitals in 12 provincial capitals or developed cities (Beijing, Jiangsu, Anhui, Jiangxi, Henan, Hubei, Shandong, Shanxi, Fujian, Heilongjiang, Xinjiang and Hainan Provinces) from East, West, South, North and Middle China were surveyed. A total of 60 questionnaires were disseminated in each region. The questionnaire was issued and received through the questionnaire star software provided by WeChat (Softonic International SA, available at <https://wechat.en.softonic.com/>). The questionnaire survey was completed between 18 October 2017 and 30 November 2017.

### Statistical methods

SPSS version 23 (IBM) was used for data management and statistical analysis. The results were listed as percentages. The chi-square test (or Fisher's exact test) was used for row multiplication lists; a *P* value of <0.05 was considered statistically significant.

## Results

### Questionnaire collection

A total of 720 questionnaires were distributed. We received a total of 290 valid questionnaires, and the questionnaire response rate was 40%.

### General information

The ratio of male to female endocrinologists involved in the survey was approximately 1:2. There were 231 cases reported from tertiary hospitals and 59 cases from secondary hospitals. The lengths of clinical experience (starting at the completion of medical education) were  $\geq 20$  years (34%), 10–20 years (32%) and <10 years (34%). The number of prolactinoma patients who had been examined by endocrinologists within the prior 6 months was 15 (5%) with more than 10 patients, 37 (13%) with 5–10 patients and 161 (56%) with 1–5 patients; 77 (27%) reported having seen no prolactinoma patients.

### Diagnosis of hyperprolactinemia

For patients with prolactin (PRL) <100 ng/mL, 22% of endocrinologists believed that a prolactinoma diagnosis could be ruled out and were more likely to suggest other causes for the hyperprolactinemia. Only 25 (9%) endocrinologists believed that PRL levels >250 ng/mL could occur in microadenoma, macroprolactinoma, macroprolactinemia or drug-induced hyperprolactinemia. Of the endocrinologists surveyed, 281 (97%) stated that thyroid-stimulating hormone (TSH) was routinely measured when elevated PRL was found. Moreover, 147 (51%) physicians considered screening for macroprolactin but lack of proper detective methods. 17% of the respondents never considered screening for macroprolactin.

### Treatment of prolactinoma

Of the endocrinologists surveyed, 169 (58%) recommended that microprolactinomas should be treated at the time of diagnosis, and 121 (42%) preferred to initiate treatment only when symptoms appeared. For macroprolactinomas, 268 (92%) chose to start treatment at diagnosis. Moreover, surgery was not recommended by 272 (94%) endocrinologists as the first choice for treating microprolactinomas.

The maximum dose of bromocriptine prescribed was between 7.5 and 15 mg/day in 82% of endocrinologists

surveyed. Only 6% of the physicians would use more than 15 mg/day. Cabergoline was not available in the mainland of China; however, physicians who were able to obtain it prescribed a maximum dose of between 2 and 3.5 mg/week, with only one physician choosing >3.5 mg/week.

For the duration of drug treatment, 202 (70%) of endocrinologists chose to withdraw medication in patients with microprolactinomas after 2–3 years of prolactin normalization, 61 (21%) chose to maintain treatment and 27 (9%) chose to discontinue medication after menopause. Regarding macroprolactinomas, 173 (60%) of physicians recommended maintenance therapy, 89 (31%) recommended withdrawal of medication 2–3 years after prolactin normalization and 28 (10%) recommended withdrawal after menopause (Fig. 1). No significant differences were detected in the subgroups of either lengths of clinical experience, levels of hospitals or number of patients referred (Table 1).

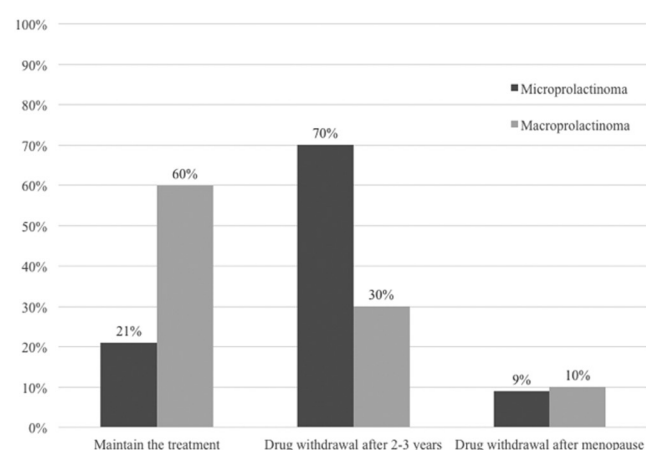
### Management of pregnancy and breastfeeding in prolactinoma patients

Of the endocrinologists surveyed, 164 (57%) considered bromocriptine to be the drug of choice for female prolactinoma patients with expectancy of pregnancy, 70 (24%) chose cabergoline and 56 (19%) considered both to be safe. In case of pregnancy during therapy with DAs, 27% of endocrinologists surveyed advocated discontinuation of treatment in patients with macroprolactinomas, whereas this rate was 63% in women with microprolactinomas (Fig. 2). Regarding breastfeeding in prolactinoma patients, 127 (44%) of the respondents believed that breastfeeding (regardless of tumor size) was allowable, 101 (35%) believed

that only patients with microadenomas should breastfeed and 62 (21%) did not recommend breastfeeding at all.

### Comparison with the other studies

We compared our results with previous two studies conducted in Brazil and the MENA region. A higher proportion of Brazilian endocrinologists recommended initiation of treatment for prolactinomas at the time of diagnosis than did those in China (75% vs 58% for microprolactinomas; 100% vs 92% for macroprolactinomas, respectively;  $P < 0.0001$ ). Endocrinologist in the MENA region tended to start treatment in microprolactinoma with symptoms (60% vs 42%,  $P < 0.0001$ ). The recommendation proportion of surgery as the first choice of treatment for microadenomas among endocrinologists was similarly low in the three studies (6, 7 and 2% for China, Brazil and MENA region). Regarding the course of treatment, Chinese endocrinologists preferred to discontinue medication 2–3 years after normalization of serum prolactin levels in microprolactinoma patients more often than did Brazilian physicians (70% vs 34%, respectively;  $P < 0.0001$ ). However, the results from the MENA region was higher than ours (82% vs 70%,  $P < 0.0001$ ). In terms of medication administration during pregnancy, the proportion of maintenance treatment in China was significantly higher than that of Brazilian physicians (26% vs 0% in macroprolactinoma and 54% vs 10% in microprolactinoma;  $P < 0.0001$ ). Same results were found in comparison with the Canadian data (6) (26% vs 0% in macroprolactinoma and 54% vs 6% in microprolactinoma;  $P < 0.0001$ ) (Table 2).



**Figure 1**  
Duration of treatment for microprolactinomas and macroprolactinomas.

### Discussion

Prolactinoma is the most common functional pituitary tumor. However, it is not commonly encountered by endocrinologists in China. There are many controversies with regard to clinical practices for diagnosis and treatment. Our survey includes responses of endocrinologists from both tertiary and secondary hospitals in different provinces in China. Most endocrinologists in China preferred prescription of bromocriptine and lacked experience in prescribing cabergoline because it was not available in the mainland of China.

In China, endocrinologists are strongly discriminatory when screening for hypothyroidism. In our study, of the surveyed physicians, 97% stated that they routinely tested TSH levels when they found that PRL was elevated. The incidence of hyperprolactinemia secondary to

**Table 1** Treatment of prolactinoma in different subgroups of endocrinologists.

	Tertiary hospitals n=231	Secondary hospitals n=59	The number of patients seen in the past 6 months		P value	Clinical experience (years)				P value
			≤5 n=238	>5 n=52		≥20 n=99	10–20 n=94	<10 n=97		
When to treat MIC	137 (59%) 94 (41%)	32 (53%) 27 (47%)	133 (56%) 105 (44%)	36 (69%) 16 (31%)	0.481	63 (64%) 36 (36%)	53 (56%) 41 (44%)	53 (55%) 44 (45%)	0.399	
When to treat MAC	216 (94%) 15 (6%)	52 (88%) 7 (12%)	220 (92%) 18 (8%)	48 (92%) 4 (8%)	0.164	93 (94%) 6 (6%)	85 (90%) 9 (10%)	90 (93%) 7 (7.2%)	0.645	
Duration of treatment in MIC	50 (22%) 157 (68%) 24 (10%)	11 (19%) 45 (76%) 3 (5%)	47 (20%) 171 (72%) 20 (8%)	14 (27%) 31 (60%) 7 (13%)	0.352	23 (23%) 63 (64%) 13 (13%)	23 (25%) 64 (68%) 7 (7%)	15 (16%) 75 (77%) 7 (7%)	0.206	
Duration of treatment in MAC	143 (62%) 65 (28%) 23 (10%)	30 (51%) 24 (41%) 5 (8%)	135 (57%) 78 (33%) 23 (10%)	38 (73%) 11 (21%) 5 (10%)	0.176	60 (61%) 31 (31%) 8 (8%)	63 (67%) 23 (25%) 8 (8.5%)	50 (51.5%) 35 (36.1%) 12 (12.4%)	0.269	
Breastfeeding	100 (43%) 85 (37%) 46 (20%)	27 (46%) 16 (27%) 16 (27%)	102 (43%) 84 (35%) 52 (22%)	25 (48%) 17 (33%) 10 (19%)	0.291	38 (38%) 40 (40%) 21 (22%)	40 (42%) 31 (33%) 23 (25%)	49 (50%) 30 (31%) 18 (19%)	0.423	

hypothyroidism was approximately 39–57% in females and 0–40% in males (7, 8, 9).

Macroprolactinemia is one reason for an increase in physiological prolactin. Use of standard immunological methodology makes it difficult to distinguish between different isoforms of prolactin. However, macroprolactin can be detected by polyethylene glycol precipitation (10). It has been reported that macroprolactinemia accounts for 15–46% of hyperprolactinemia cases (11). Because of its large molecular weight, macroprolactin cannot exert its biological effects by binding to receptors through blood vessel walls (12). Therefore, macroprolactinemia generally does not have the typical clinical manifestations of hyperprolactinemia. Thus, screening for macroprolactin may be significant for determining reasonable diagnosis and treatment. However, this screening in China has not yet been popularized, and no effective detection method has been established. Our survey found that approximately one-fifth of the endocrinologists surveyed did not understand the biology of macroprolactin. Therefore, the knowledge of macroprolactin needs to be improved to avoid inappropriate treatment.

Drug-induced hyperprolactinemia is also one of the causative factors for elevated PRL that needs to be identified. Common drugs that cause elevation of PRL include metoclopramide, antipsychotics, antidepressants, estrogens and cocaine. The main cause of drug-induced hyperprolactinemia is the dopamine receptor antagonistic effect. Moreover, these drugs can increase prolactin release factors such as serotonin and can elevate prolactin levels (13). Estrogen can bind to receptors on prolactin cell surfaces to promote cell proliferation and prolactin secretion, and, thus, could act directly on the hypothalamus to inhibit the release of dopamine and lead to prolactin elevation (14). A detailed medical history is the key to diagnosing drug-induced hyperprolactinemia. Its treatment should be based on a comprehensive assessment of the primary disease based on rational adjustment of drugs and, if necessary, addition of DAs (15).

Whether or not medication withdrawal after menopause is advisable in prolactinomas has not been determined. It has been suggested that the clinical symptoms of menstrual disorders and infertility caused by hyperprolactinemia are of no clinical significance in postmenopausal women, and prolactin levels will decline along with the level of estrogen decline after menopause (16). In addition, the long-term use of drugs may increase adverse reactions such as impulsive control disorders and other behavioral changes (17). In contrast, there are also views supporting the treatment of postmenopausal

**Table 2** Comparison with other studies.

		China	Brazil	MENA
		n=290	n=721	n=168
When to treat MIC	Always	169 (58%)	541 (75%) <sup>***</sup>	67 (40%) <sup>***</sup>
	Only in the presence of symptoms	121 (42%)	180 (25%)	101 (60%)
When to treat MAC	Always	268 (92%)	721 (100%) <sup>***</sup>	156 (93%) <sup>n.s.</sup>
	Only in the presence of symptoms	22 (8%)	0 (0%)	12 (7%)
Duration of treatment in MIC	Maintain the treatment	61 (21%)	346 (48%) <sup>***</sup>	10 (6%) <sup>***</sup>
	Drug withdrawal after 2–3 years	202 (70%)	245 (34%)	138 (82%)
	Drug withdrawal after menopause	27 (9%)	130 (18%)	20 (12%)
Duration of treatment in MAC	Maintain the treatment	173 (60%)	505 (70%) <sup>**</sup>	84 (50%) <sup>n.s.</sup>
	Drug withdrawal after 2–3 years	89 (30%)	144 (20%)	67 (40%)
	Drug withdrawal after menopause	28 (10%)	72 (10%)	17 (10%)
Pregnancy in MIC	Discontinue the treatment	183 (63%)	505 (70%) <sup>***</sup>	108 (64%) <sup>n.s.</sup>
	Change the drug	32 (11%)	216 (30%)	
	Maintain the treatment	75 (26%)	0 (0%)	
Pregnancy in MAC	Discontinue the treatment	79 (27%)	418 (58%) <sup>**</sup>	62 (37%) <sup>*</sup>
	Change the drug	54 (19%)	231 (32%)	
	Maintain the treatment	157 (54%)	72 (10%)	
Breastfeeding	Both MIC and MAC	127 (44%)	260 (36%) <sup>*</sup>	84 (50%) <sup>n.s.</sup>
	Only in MIC	101 (35%)	317 (44%)	50 (30%)
Surgery for first choice in MIC	No	62 (21%)	144 (20%)	34 (20%)
		18 (6%)	51 (7%) <sup>n.s.</sup>	4 (2%) <sup>n.s.</sup>

The data of Brazil and MENA are derived from Ref. (4, 5) respectively. P values using the Chi-square test (or Fisher's exact test).

\*P<0.05; \*\*P<0.001; \*\*\*P<0.001.

MAC, macroprolactinoma; MIC, microprolactinoma.

hyperprolactinemia. On the one hand, macroadenoma is much more common in menopausal patients at the onset of prolactinoma. On the other hand, long-term hyperprolactinemia might increase osteoporosis risk (18).

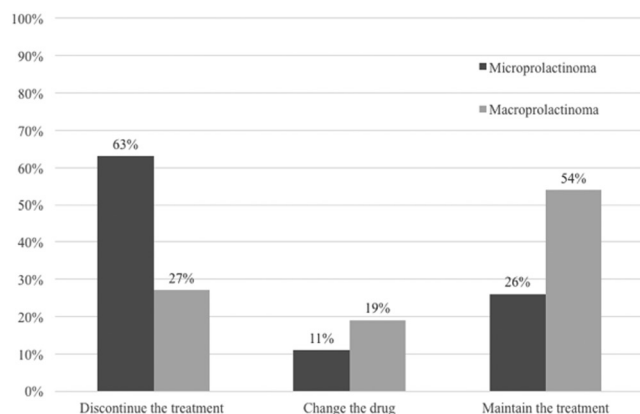
Recent data have shown that transsphenoidal surgery may lead to normal PRL levels in the postoperative period in 71–100% of microprolactinoma patients with very low postoperative complication rates (19). Our previous work also showed a high remission rate in female prolactinoma patients, especially in microadenoma patients, after surgery (20). Transsphenoidal surgery might be an alternative method to achieve long-term remission and avoid the side effects of medical therapy in prolactinoma patients. Patient preference and surgeon's experience should be considered as indications for surgery in patients with prolactinoma (19, 21, 22). It seemed that most endocrinologists were conservative on surgery of prolactinoma.

Regarding pregnancy in prolactinoma, medication was recommended to be continued in the first trimester of pregnancy in order to maintain luteal function in Chinese expert consensus. However, in recent guideline of prolactinoma, women with prolactinomas have to

be instructed to discontinue DA as soon as pregnancy is confirmed (1). Bromocriptine was considered safe to prescribe to pregnant prolactinoma patients, and rates of spontaneous abortion, intrauterine fetal death and fetal malformation after pregnancy were similar to obstetric anomalies occurring in healthy people (23, 24). Likewise, cabergoline administration did not increase the incidence of pregnancy-related adverse events; however, there was relatively less clinical evidence available for cabergoline than for bromocriptine (25, 26, 27). There was no evidence found that breastfeeding stimulated tumor growth. For females who were willing to breastfeed, it was generally recommended that they be prescribed DAs at the end of lactation unless a pregnancy-induced tumor growth required treatment (28).

### Limitations

There were several limitations to this study. The clinical experience with prolactinoma management in the surveyed physicians was generally insufficient. Furthermore, due to the self-reported survey, the results may not reflect actual practice.



**Figure 2**  
Management during pregnancy.

## Conclusion

This is the first study to investigate the knowledge and practice of endocrinologists in China on management of prolactinoma. We found that the current clinical treatment of prolactinoma was not uniform. Therefore, it is necessary to strengthen the training of endocrinologists in order to improve clinical diagnosis and treatment practices, and, in turn, to improve outcomes in prolactinoma patients.

### Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-18-0250>.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors. All participants provided an informed explicit consent to participate electronically before they proceeded to participation in the survey. All data are collected anonymously in the survey.

### Author contribution statement

Lijin Ji and Na Yi wrote the manuscript. Qi Zhang conducted the statistical analysis. Xiaoxia Liu and Shuo Zhang modified and delivered the questionnaire. Bin Lu and Hongli Shi designed the study and revised the manuscript. All authors approved the final manuscript.

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