Hyperprolactinemia: A 12-Year Retrospective Study at Gynecologic Endocrinology Unit, Siriraj Hospital

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Background: *Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic-pituitary axis. To date, no available data about hyperprolactinemia in Thai women has been published.*
Objective: *To determine clinical and laboratory findings of Thai female patients with different etiology of hyperprolactinemia, as well as the response of treatment, recurrence, and pregnancy after treatment.*
Material and Method: *Medical records of 139 female patients with the diagnosis of hyperprolactinemia in Gynecologic Endocrinology Unit, Siriraj Hospital between January 1, 1999 and December 30, 2011 were retrospectively reviewed after the study protocol was approved by Siriraj Institutional Review Board. The data was analyzed to determine patient demographic data, presenting symptoms, duration of symptoms, initial serum prolactin levels, causes, imaging studies, treatment, treatment outcomes, and adverse events.*
Results: *Ninety-seven female patients with hyperprolactinemia were included in the study. Mean age at diagnosis was 31.8±7.7 years. Amenorrhea was the most common presenting symptom (49.5%) followed by galactorrhea (44.3%). Median initial serum prolactin level was 117 ng/mL (25.1-1,624 ng/mL). Pituitary adenoma is the most common cause (40.2%) followed by idiopathic hyperprolactinemia (37.1%). Microadenomas were found in 74.3% of pituitary adenoma. The median size of the tumor was 9 mm. Medical treatment was given to 79 (88.8%) patients. Bromocriptine was given to 66 patients. Mean of maximum dose of bromocriptine was 5.8 mg. Median duration of treatment was 35.8 months. Adverse events were reported in 24.2% of patients, dizziness was the most common adverse event. Median time to normalize serum prolactin level was 3.8 months. In 29 patients who desired pregnancy, eight patients got pregnant. Median time to pregnancy was 25.9 months. Patients with macroadenoma had significantly higher prolactin level than those with microadenoma ($p = 0.024$). Patients with galactorrhea had the shortest duration of symptom ($p = 0.010$). There were no statistically significant difference in symptoms, duration of symptoms, and initial prolactin level between patients with and without pituitary adenoma. Patients with pituitary adenoma needed higher doses ($p = 0.009$) and longer duration of treatment ($p = 0.007$) than those without a tumor. Normalization of prolactin level and recurrence rate was not different between the two groups ($p = 0.056$ and 0.374). Log rank test showed that the time to normalize and survival time of recurrence were not significantly different between patients with and without a tumor ($p = 0.136$ and 0.146, respectively).*
Conclusion: *Amenorrhea was the most common presenting symptom in Thai hyperprolactinemic females, who attended Siriraj gynecologic endocrinology unit, followed by galactorrhea. Pituitary adenoma is the most common cause followed by idiopathic hyperprolactinemia. Patients with pituitary adenoma needed higher doses and longer duration of treatment than those without a tumor.*

Keywords: *Hyperprolactinemia, Pituitary adenoma, Thai, Female*

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Hyperprolactinemia is one of the most common endocrine disorder of the hypothalamic-pituitary axis[1]. It occurs more commonly in women. The prevalence of hyperprolactinemia varies in different population ranging from 0.4% in an unselected normal population up to 17% in women with reproductive disorders[2]. The diagnosis is made when serum prolactin levels are above the normal value established for the laboratory used.

The causes of hyperprolactinemia are divided into three categories, physiological, pharmacological, and pathological causes[1]. Pregnancy and lactation are the examples of physiological hyperprolactinemia. Certain drugs can also cause hyperprolactinemia

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such as antipsychotics, antidepressants, antiemetics. Prolactinomas account for 25 to 30% of functioning pituitary tumors and are the most common cause of pathological hyperprolactinemia[1]. They are classified according to size; tumors smaller than 10 mm in diameter are defined as microprolactinoma and larger tumors (10 mm) are defined as macroprolactinoma. The clinical presentation of hyperprolactinemia is related to hypogonadism, galactorrhea, and symptoms caused by mass effects of the tumor. Women with hyperprolactinemia may present with oligomenorrhea, amenorrhea, infertility, decreased libido, and habitual abortion. It is essential to rule out physiological and pharmacological causes of hyperprolactinemia. A detailed medical history, clinical examination and laboratory tests including tests for pregnancy, renal and thyroid function are all vital. When physiological and pharmacological causes are excluded, pituitary imaging is undertaken by magnetic resonance imaging (MRI) or computerized tomography (CT) scanning. Magnetic resonance imaging of the pituitary with gadolinium enhancement appears to provide the best anatomic detail[3]. The coned down view of plain skull x-ray is insensitive[4].

The medication of choice is dopamine agonists. Bromocriptine is the first of the dopamine agonist drugs to be introduced and widely used. Cabergolide and quinagolide have similar efficacy to bromocriptine but are associated with fewer adverse effects than bromocriptine[1,5,6].

Up to date, no available data about hyperprolactinemia in Thai women has been published. The objectives of the present study were to determine clinical and laboratory findings of Thai female patients with different etiology of hyperprolactinemia, as well as the response of treatment, recurrence and pregnancy after treatment.

Material and Method

This retrospective study was conducted between December 2012 and April 2013 at the Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The study was conducted in accordance with the Helsinki Declaration and the study protocol was approved by the Siriraj Institutional Review Board.

Hyperprolactinemia in our institute is defined as serum prolactin levels higher than 25 ng/mL. The normal prolactin levels in women established for the laboratory used in our institute is 4.79 to 23.3 ng/mL. Before 2002, according to the unit guideline, pituitary imaging is compulsory only when the prolactin level is higher than 100 ng/mL.

Medical records of 139 women with diagnosis of hyperprolactinemia, who were registered between January 1, 1999 and December 30, 2011, were reviewed. Of these, 97 cases possessed complete medical history, physical examination, adequate investigation for diagnosis, and treatment were eligible for the present report.

The data were analyzed using SPSS for windows version 17. Data were present in mean ± standard deviation (SD), median (minimum, maximum), number (n) and percent, or hazard ratio (HR) and 95% confidence interval (CI), as appropriate. Continuous data were compared using Student's t-test, one-way analysis of variance (ANOVA), Mann-Whitney U test or Kruskal Wallis test as appropriate. Categorical data were compared using Chi-square test, Fisher's exact test or Poisson test. The rates of normalization of prolactin level and recurrent hyperprolactinemia were estimated using Kaplan-Meier method and the differences in the results between adenoma and non-adenoma group were analyzed using log-rank test. Cox regression analysis was used to evaluate the effect of adenoma on rates of normalized and recurrent hyperprolactinemia. All tests were two-tailed and a $p<0.05$ was considered to indicate a statistically significant difference.

Results

Ninety-seven female patients with hyperprolactinemia were included in the present study. Mean age at diagnosis and other demographic data are presented in Table 1. Median initial serum prolactin level was 117 ng/mL (range 25.1-1,624.0 ng/mL). The most common presenting symptoms were amenorrhea, galactorrhea, and oligomenorrhea respectively. Clinical features and causes of hyperprolactinemia are shown in Table 2. Pituitary adenoma is the most common cause (40.2%) followed by idiopathic hyperprolactinemia (37.1%). Microadenomas were found in 74.3% (29/39) of pituitary adenoma. The median size of tumor was 9 mm. The details of treatment are presented in Table 3. Medical treatment was given to 79 (88.8%) patients. Bromocriptine was given to 66 patients with a mean maximum dose of 5.8 mg. Median duration of treatment was 35.8 months (range 1.2-167.1 months).

The outcomes of bromocriptine treatment are shown in Table 4. Median time to normalize serum

Table 1. Demographic data (n = 97)

Characteristic	n	
Age (year)	97	31.82±7.73
Body mass index (kg/m^2)	75	22.17±4.04
Nulliparity	89	64 (71.9%)
Fertility need	82	34 (41.5%)
Underlying disease	97	
No known underlying disease		72 (74.2%)
Psychiatric disorder		12 (12.4%)
PCOS		4 (4.1%)
Thyroid disease		3 (3.1%)
Other*		6 (6.2%)

* Diabetes melitus = 1, hypertension = 1, liver disease = 1, premature ovarian failure = 1, asthma = 1, chronic motor tics = 1
Data was presented in mean ± SD and n (%)
PCOS = polycystic ovary syndrome

Table 2. Clinical features (n = 97)

Clinical feature	n (%)
Presenting symptoms	
Amenorrhea	48 (49.5)
Galactorrhea	43 (44.3)
Oligomenorrhea	6 (6.2)
Duration of symptoms* (months)	7.00 (0.03, 288.00)
Initial prolactin level* (ng/mL)	117.0 (25.1, 1,624.0)
Cause	
Drug induced**	17 (17.5)
Systemic disorder: PCOS	4 (4.1)
Hypothalamic-pituitary stalk damage	1 (1.0)
Pituitary adenoma	39 (40.2)
Microadenoma	29 (29.9)
Macroadenoma	10 (10.3)
Idiopathic hyperprolactinemia	36 (37.1)
Imaging investigation (n = 67)	
Positive plain film skull (n = 13)	4 (30.1)
Positive computerized tomography (n = 15)	6 (40.0)
Positive magnetic resonance imaging (n = 39)	30 (76.9)
Pituitary adenoma in size* (mm), n = 20	9.0 (2.0, 27.0)

* Data was presented in median (minimum, maximum)
** Drug induced: antipsychotic drug = 13 (risperidone = 4, haloperidol = 3, perphenazine = 3, phenobarbital = 1), domperidone = 2, omeprazole = 1, oral contraceptive pills = 1
PCOS = polycystic ovary syndrome

prolactin level was 3.8 months. In 29 patients who desired pregnancy, eight patients became pregnant with a median time of 25.9 months. Prolactin levels and duration of symptoms in different presenting symptoms,

Table 3. Treatment features

Treatment feature	n	
Treatment	97	
Observation and advice		17 (17.5%)
Medical		79 (88.8%)
Bromocryptine		68 (76.4%)
Oral contraceptive pills		5 (5.6%)
Progestin		6 (6.7%)
Surgery		1 (1.1%)
Bromocryptine starting dose	66	
Step up protocol*		42 (63.6%)
1.25 mg/day		4 (6.1%)
2.5 mg/day		8 (12.2%)
5 mg/day		12 (18.1%)
Bromocriptine maximum dose (mg)	66	5.8±3.7

* Step up protocol was started treatment with bromocriptine 1.25 mg/day then step up with 1.25 mg/day everyweek
Data was presented in n (%) and mean ± SD

causes and pituitary adenoma are presented in Table 5. Macroadenoma had significantly higher prolactin level than microadenoma (p = 0.024). Patients with galactorrhea had the shortest duration of symptom (p = 0.01). Thus, concern about galactorrhea rather than menstrual changes made the patients seek diagnosis earlier. Drug induced hyperprolactinemia had the shortest duration of symptoms before seeking medical advice compared to other causes (p = 0.049). There were no statistically significant differences in symptoms, duration of symptoms and initial prolactin level between patients with pituitary adenoma and non-pituitary adenoma as shown in Table 6. However, patients with pituitary adenoma need higher doses (p = 0.009) and longer duration of treatment (p = 0.007) than those without a tumor. The rates of normalized prolactin level and recurrence were not different between the two groups (p = 0.056 and 0.374, respectively).

Log rank test showed that the time to normalization and survival time of recurrence were not significantly different between patients with or without a tumor (p = 0.136 and 0.146, respectively). Fig. 1 shows the normalized prolactin level rate and Fig. 2 shows the recurrence rate after treatment cessation using Kaplan-Meier method. Cox regression analysis showed no association between patients with or without adenoma, the hazard ratio of normalized prolactin level and recurrence after cessation of treatment were 1.61 (95% CI 0.86-3.03; p = 0.136) and 2.26 (95% CI 0.75-6.76; p = 0.146), respectively as shown in Table 7. Patients with adenoma had a trend to use shorter time to normalize prolactin level after

Table 4. Bromocriptine treatment results

Treatment result	n	n (%)
Total follow-up time (month after start treatment)	66	40.1 (1.2, 167.1)
Treatment duration (month)	66	35.8 (1.2, 167.1)
Normalization of prolactin level	66	42 (63.6)
Time to normalization (months after start treatment)	42	3.8 (0.5, 65.4)
Recurrence after normalization	42	32 (76.2)
Time to recurrence (months after normalization)	32	10.6 (1.84, 53.65)
Medication cessation after normalized	42	30 (71.4)
Recurrence after medical cessation	30	14 (46.7)
Time to recurrence (months after medication cessation)	14	3.9 (0.5, 23.0)
Adverse event	66	16 (24.2)
Dizziness		11 (16.7)
Nausea and/or vomiting		3 (4.5)
Headache		1 (1.5)
Allergic rash		1 (1.5)
Pregnancy*	29	8 (27.6)
Time to pregnancy	8	25.9 (1.5, 68.3)

* In 29 cases that need fertility, 8 cases became pregnant: Poisson test = 8/1,286 person-month = 6.2/1,000 person-month (95% CI: 2.7, 12.2)
Data was presented in median (minimum, maximum) and n (%)

Table 5. Association of clinical features

Clinical feature	n	Prolactin level (ng/mL)	p-value	Duration of symptom (months)	p-value
Presenting symptom	97		0.302*		0.010*
Amenorrhea	48	129.1 (31.6, 1,624.0)		10.5 (1.0, 288.0)	
Galactorrhea	43	121.1 (25.1, 1,163.0)		4.0 (0.03, 168.0)	
Oligomenorrhea	6	92.2 (56.0, 115.0)		9.0 (2.0, 60.0)	
Cause	97		0.247*		0.049*
Drug induce	17	121.1 (38.0, 294.2)		2.0 (0.03, 60)	
Systemic disorder	4	47.2 (31.6, 200.0)		9.5 (6.0, 120.0)	
Hypothalamic-pituitary stalk damage	1	138.2		132.0	
Pituitary adenoma	39	152.9 (25.1, 1,624.0)		9.0 (0.03, 240.0)	
Idiopathic	36	85.5 (25.3, 1,163.0)		6.5 (0.03, 288.0)	
Pituitary adenoma	39		0.024**		0.554**
Microadenoma	29	118.0 (25.1, 540.1)		6.0 (0.03, 108.0)	
Macroadenoma	10	315.0 (61.4, 1,624.0)		12.0 (2.0, 72.0)	

* Kruskal Wallis test, ** Mann-Whitney test
Data was presented in median (minimum, maximum)

treatment and had shorter time to recurrence after medical cessation without difference. This may be due to a small number of sample sizes.

Discussion

The increase in prolactin levels results in effects equivalent to those observed during the postpartum period. Prolactin is a lactogenic hormone promoting milk formation. The antigonadal effect of prolactin results in anovulation and even more profoundly hypogonadotropic hypoganadism[5], depending on the extent to which gonadotropin secretion is suppressed. The clinical presentations of hyperprolactinemia are related to hypogonadism, galactorrhea, and the symptoms caused by mass effects of the tumor such as headache and visual loss.

Table 6. Clinical features between pituitary adenoma and non-pituitary adenoma causes

Clinical feature	n	Pituitary adenoma (n = 39)	n	Non-pituitary adenoma (n = 58)	p-value
Galactorrhea		17 (43.6%)		33 (56.9%)	0.199*
Amenorrhea		26 (66.7%)		30 (57.7%)	0.144*
Oligomenorrhea		1 (2.6%)		5 (8.6%)	0.225*
Duration of symptoms (months)		9.0 (0.03, 240.0)		6.0 (0.03, 288.0)	0.213**
Initial prolactin level (ng/mL)		152.9 (25.1, 1,624.0)		95.1 (25.3, 1,163.0)	0.079**
Treatment					0.071*
Observation and advice		2 (5.1%)		15 (25.9%)	
Medical		36 (92.3%)		43 (74.1%)	
Surgery		1 (2.6%)		0 (0%)	
Bromocryptine max dose (mg/day)	35	6.8±4.2	31	4.6±2.5	0.009***
Treatment duration (month)	35	20.2 (2.1, 167.1)	31	7.9 (0.9, 96.1)	0.007**
Total follow-up time (month)	35	40.7 (2.1, 167.1)	31	33.5 (1.2, 136.4)	0.119**
Normalization of prolactin level	35	26 (74.3%)	31	16 (51.6%)	0.056*
Time to normalization (months after start treatment)	26	3.02 (0.5, 65.4)	16	5.5 (1.8, 23.5)	0.219**
Recurrence after normalization	26	21 (80.8%)	16	11 (68.8%)	0.374*
Stop treatment after normalization	26	17 (65.4%)	16	13 (81.3%)	0.168*
Time to recurrence (months after cessation medication)	9	3.4 (1.0, 23.0)	5	5.6 (0.5, 21.0)	0.797**
Pregnancy	16	5 (31.3%)	13	3 (23.1%)	0.317*

* Chi-square test, ** Mann-Whitney test, *** t-test
Data was presented in n (%), mean ± SD, and median (minimum, maximum)

Table 7. Survival analysis in bromocriptine treatment group

	n	Event (%)	Hazard ratio (95% CI)	p-value*
Normalization of prolactin level after treatment	66			0.136
Non-adenoma	31	16 (51.6)	1	
Adenoma	35	26 (74.3)	1.61 (0.86, 3.03)	
Recurrence after cessation of treatment	30			0.146
Non-adenoma	13	5 (38.5)	1	
Adenoma	17	9 (52.9)	2.26 (0.75, 6.76)	

* Cox regression analysis: hazard ratio of adenoma
Data was presented in n (%) and Hazard ratio (95% CI)

Hyperprolactinemia is seen in approximately 15% of cases of secondary amenorrhea[8,9] and 75% of patients with both amenorrhea and galactorrhea[6]. Two thirds of hyperprolactinemic women were absence of galactorrhea[4,5], which may result from inadequate estrogenic or progestogenic priming of the breast[4]. The structural heterogeneity of prolactin offers another possible explanation. The present study showed that amenorrhea (49.5%) was the most common presenting symptom in female hyperprolactinemia followed by galactorrhea (44.3%). Fourteen cases (14.4%) presented with both amenorrhea and galactorrhea. No case was presented with symptoms of mass effect of the tumor. Patients with galactorrhea were more likely to see physicians to seek the diagnosis than those with amenorrhea.

The most common causes of pathological hyperprolactinemia in this study were pituitary adenoma (40.2%) and idiopathic hyperprolactinemia (37.1%). Prolactinomas account for 25 to 30% of pituitary adenomas and are the most common cause of hyperprolactinemia[1,6,10]. There are many causes of hyperprolactinemia that should be ruled out before the diagnosis of pathological hyperprolactinemia

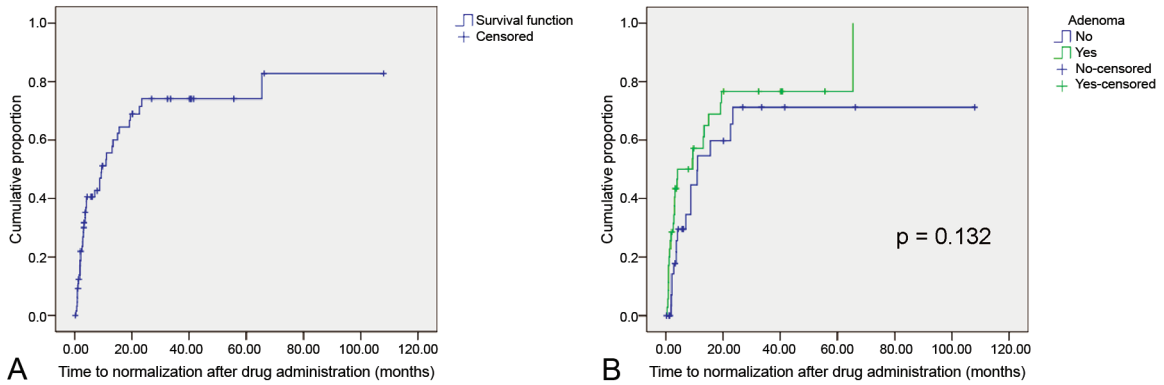

Fig. 1 Normalization of prolactin level after bromocriptine treatment.
Kaplan-Meier curve for time in months to normalize prolactin level. Axis X represented time (month) and Axis Y represented the cumulative proportion of normalized patients. (A) Overall median time to normalize prolactin level was 9.5 months. (B) Comparing pituitary adenoma with non-pituitary adenoma group, normalization occurred in 26 of 35 patients and 16 of 31 patients with median time to normalize prolactin level of 3.9 and 4.8 months respectively (log rank test p-value = 0.132).

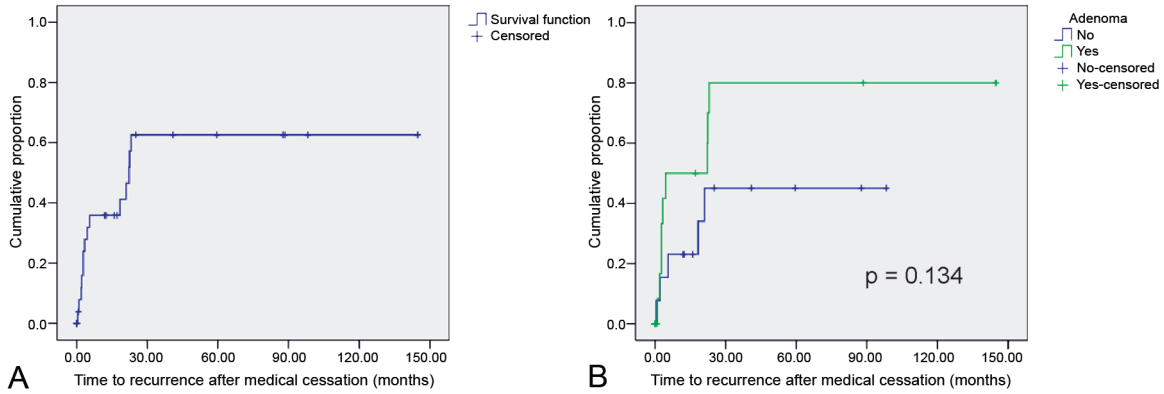

Fig. 2 Recurrence of hyperprolactinemia after treatment cessation.
Kaplan-Meier curve for time in months to recurrence after bromocriptine cessation. Axis X represented time (month) and Axis Y represented the cumulative proportion of recurrent patients. (A) Overall median time to recurrence was 22.3 months. (B) Comparing pituitary adenoma with non-pituitary adenoma group, recurrence occurred in 9 0f 17 patients and 5 of 13 patients respectively (log rank test p-value = 0.134). Median time to recurrence was not significant difference between groups.

was made. In the present study, pharmacological hyperprolactinemia was found in 17.5% of the cases. Antipsychotic drugs were the most common cause of drug-induced hyperprolactinemia. Several other systemic disorders can cause hyperprolactinemia. Mild hyperprolactinemia is sometimes seen in a proportion of cases of polycystic ovary syndrome (PCOS)[5,11,12]. Primary hypothyroidism is commonly associated with mild hyperprolactinemia due to the stimulatory effect of thyroid releasing hormone (TRH) on lactrotrophs[5,13] and can be normalized by thyroid hormone replacement[7]. Chronic renal failure causes hyperprolactinemia both by reducing excretion and by effecting dopamine function[6]. Lesions affecting the hypothalamus and pituitary stalk disconnection such as craniopharyngiomas, germinomas, gliomas, and nonfunctioning adenomas also result in prolactin elevation. However, the prolactin levels in these which patients are rarely greater than 250 ng/mL[8]. In this present study, there was one case of craniopharyngioma which presented with hyperprolactinemia. The initial prolactin level was 138.2 ng/mL. Only four cases of PCOS were associated with hyperprolactinemia.

Pituitary imaging was performed in 67 cases. Before 2002, the coned down view of plain skull x-ray was performed in patients who could not afford MRI

or CT scan. The coned down view of plain skull x-ray was performed in thirteen cases and four of them showed abnormal finding suggesting pituitary adenoma. Since the coned down view of plain skull x-ray is insensitive, the prevalence of pituitary tumors was underestimated. After the government health policy called "Universal coverage policy" started in 2002, MRI or CT scan was available for pituitary imaging. MRI is the most sensitive method to detect pituitary adenoma (Table 2). Thirty of 39 cases who had MRI performed showed positive finding of pituitary adenoma whereas only 6 in 15 cases and 4 in 13 cases who had CT scan performed and the coned down view of plain skull x-ray did. However, microadenomas size less than 5 mm may not be visualized with MRI or CT scan and are classified as idiopathic hyperprolactinemia[6].

Dopamine agonists have become the treatment of choice for the majority of patients with hyperprolactinemia. Bromocriptine is the only dopamine agonist available in Thailand. It was the first dopamine agonist to be used in clinical practice. It is effective in normalizing serum prolactin levels and restoring gonadal function in 80 to 90% of patients with microprolactinoma and nearly 70% of those with macroprolactinomas, with varying degree of tumor shrinkage[13,14,17,18]. In this present study, 63.6% of patients treated with bromocriptine resumed normal serum prolactin levels after a median of 3.8 months of treatment with a mean maximum dose of 5.8 mg. The remission rate of 63.6% is similar to that observed in a recent multicenter study (67.1%)[10]. Two patients were lost to follow-up before normalizing serum prolactin levels. The common side effects are postural hypotension, headache, nausea, and vomiting. In one previous report, nearly 60% of patients developed side effects[11] while in the present study, the side effects were reported in only 24.2% of patients. Side effect rate in the present study was also lower than those in other previous studies[19,20]. The reason may be the initial low dose of bromocriptine used and very gradual dose escalation in the present study. Bromocriptine was started with 1.25 mg/day and stepped up by 1.25 mg per week. Interestingly, administration of bromocriptine via the intravaginal route can reduce gastrointestinal side effects compared with the oral route[7].

For a median follow-up time of 40.1 months, recurrent rate of hyperprolactinemia after normalization was 76.2% with a median time to recurrence of 10.6 months. Eleven patients had rising of prolactin level while tapering dose of bromocriptine and finally after increasing bromocriptine dosage, all had normalization of prolactin level. After a median treatment time of 22.3 months, 30 patients stopped bromocriptine and 14 (46.7%) patients had recurrence with the median time to recurrence of 3.9 months after bromocriptine cessation. The evidence from the previous study suggested that relapse usually occurred within three months of bromocriptine suspension[12]. The recurrence rates of hyperprolactinemia after bromocriptine withdrawal observed in other studies varied considerably between 50 and 93%[21-27]. This wide range of discrepancy may relate to duration of treatment, duration of follow-up, pretreatment prolactin levels, and the mixed data of microprolactinoma and macroprolactinoma. Most studies had a mean duration of bromocriptine treatment of 24 months. In the present study, the median treatment time of 30 patients who stopped treatment was 22.3 months, which was similar to other previous studies. This present study had a slightly lower recurrence rate (46.7%) than that in the previous studies[12,21-27].

The duration of treatment may be an important determinant of remission[12,13]. Moriondo et al reported an initial recurrent rate of 89% following 12 months of treatment, but in those patients that recurred, a further 12 months of treatment reduced recurrent rate to 78% of patients with microprolactinoma[13]. Cabergolide is a long active dopamine agonist that is more effective than bromocriptine and has fewer side-effects[6,10,14]. A prospective study addressed that the outcome of withdrawing cabergolide treatment showed recurrent rate of only 24% for non-tumoral hyperprolactinemia, 31% for microadenomas, and 36% for macroadenomas, over a two to five years period[15]. The evidences from previous studies and the present study suggest that dopamine agonist treatment may not be required indefinitely in hyperprolactinemic patients. It would be reasonable to consider dose reduction or treatment withdrawal after 2-5 years of dopamine agonist treatment[1,12,15].

Dopamine agonist treatment restores ovulation in about 90% of women with anovulatory infertility secondary to hyperprolactinemia[14]. In 29 patients wishing to try pregnancy, eight (27.6%) patients became pregnant with a median time of 25.9 months corresponding to 6.2/1,000 person-month (95% CI: 2.7, 12.2). The pregnancy rate in the present study is quite similar to that previously reported by Biswas M et al (30.3%). The pituitary gland is normally

enlarged significantly during pregnancy. There is a risk that a prolactinoma may enlarge and compress the optic nerve. A large meta-analysis have shown that the risk of a clinically significant expansion of a microprolactinoma is less than 2%, although for a macroprolactinoma the risk may be as high as 15 to 30%[16]. During pregnancy, women with prolactinoma should be monitored closely for symptoms and signs suggestive of tumor enlargement[1,12]. Symptomatic tumor enlargement during pregnancy is usually best treated with bromocriptine rather than surgery[1]. Bromocriptine has no apparent risk of congenital abnormality or miscarriage, or childhood development[17].

Oral contraceptive pills and progestin were used in 11 patients with idiopathic hyperprolactinemia. Progestin treatment is appropriate for hyperprolactinemic woman with anovulation who does not desire pregnancy. Oral contraceptive pills may be used in hypoestrogenic woman with idiopathic hyperprolactinemia who does not wish to become pregnant, and for prevention of osteoporosis and restoration of menstruation when galactorrhea is not a major problem. Hypoestrogenic women with microprolactinoma may be treated with oral contraceptive pills if they are intolerant to dopamine agonist. The previous published study on patients with prolactinoma who were treated with oral contraceptive pills has not shown any substantial risk for tumor enlargement[18]. Periodic measurement of prolactin level should be done in patients who use oral contraceptive pills[19].

Seventeen patients with drug-induced hyperprolactinemia did not receive any medical treatment. Dopamine agonists are not indicated for hyperprolactinemia due to antipsychotic drugs[20]. Psychiatric management can be adjusted and drugs which have lesser effect on prolactin secretion should be substituted[21,22]. If patients have amenorrhea, hormone replacement therapy can be used[23].

Some limitation of this study should be noted. This is a retrospective study so some data are missing. The prevalence of pituitary microadenoma may be underestimated and the prevalence of idiopathic hyperprolactinemia may be overestimated since some patients had the coned down view of plain skull x-ray that is insensitive, and microadenoma size less than 5 mm may not be visualized with MRI or CT scan. There was no protocol about proper time to follow-up serum prolactin level. Therefore, there were different periods to repeat the prolactin level in each patient. This study included only female patients who registered at the Gynecologic Endocrinology Unit. Thus, there were other Thai patients with hyperprolactinemia who attended in other departments i.e. department of surgery, medicine, or ophthalmology which might have different demographic data, causes of hyperprolactinemia, treatment, and treatment outcome.

In conclusion, the most common presenting symptoms of hyperprolactinemia in females were amenorrhea and galactorrhea. Pituitary adenoma and idiopathic hyperprolactinemia were the two most common causes of pathologic hyperprolactinemia. Bromocriptine is the drug of choice for pituitary adenoma and idiopathic hyperprolactinemia. Patients with pituitary adenoma need higher doses and longer duration of treatment than those without a tumor.

Potential conflicts of interest

None.

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ภาวะโปรแลกตินในเลือดสูง: การศึกษาย้อนหลัง 12 ปี ที่หน่วยต่อมไร้ท่อทางนรีเวช โรงพยาบาลศิริราช

รติกร แซ่จ้อง, จงดี แดงรัตน์, กิติรัตน์ เตชะไตรศักดิ์, สุรศักดิ์ อังสุวัฒนา, มณี รัตนไชยานนท์, ประสงค์ ตันมหาสมุทร

ภูมิหลัง: *โปรแลกตินในเลือดสูงเป็นภาวะผิดปกติของแกนฮัยโปธะละมัส-ต่อมใต้สมอง ที่พบได้บ่อย ในปัจจุบันยังไม่มีรายงานภาวะนี้ในสตรีไทย*

วัตถุประสงค์: *ศึกษาลักษณะทางคลินิกและสิ่งตรวจพบทางห้องปฏิบัติการ รวมถึงผลต่อการรักษา การกลับเป็นซ้ำ และการตั้งครรภ์ภายหลังการรักษาของสตรีไทยที่มีภาวะโปรแลกตินในเลือดสูง*

วัสดุและวิธีการ: *รวบรวมข้อมูลผู้ป่วยย้อนหลังจากเวชระเบียนของผู้ป่วยหญิงที่ได้รับการวินิจฉัยภาวะโปรแลกตินในเลือดสูง 139 ราย ที่มารับบริการที่คลินิกต่อมไร้ท่อทางนรีเวช โรงพยาบาลศิริราช ระหว่างวันที่ 1 มกราคม พ.ศ. 2552 ถึง 30 ธันวาคม พ.ศ. 2554 หลังจากได้รับการรับรองจากคณะกรรมการจริยธรรมการวิจัยในคน ของคณะแพทยศาสตร์ศิริราชพยาบาล ข้อมูลจะถูกรวบรวมและวิเคราะห์เพื่อศึกษาลักษณะพื้นฐานของผู้ป่วย อาการแสดง ระยะเวลาของอาการ ระดับโปรแลกติน สาเหตุ การศึกษาภาพวินิจฉัย การรักษา ผลการรักษา และอาการข้างเคียง*

ผลการศึกษา: *มีผู้ป่วย 97 ราย ที่มีข้อมูลครบ อายุเฉลี่ย 31.8±7.7 ปี อาการขาดระดูเป็นอาการที่นำผู้ป่วยมาพบแพทย์ที่พบบ่อยที่สุด (ร้อยละ 49.5) ตามด้วยอาการน้ำนมไหล (ร้อยละ 44.3) ค่ามัธยฐานของระดับโปรแลกตินเท่ากับ 117 นาโนกรัมต่อมิลลิลิตร (25.1-1,624 นาโนกรัมต่อมิลลิลิตร) เนื้องอกต่อมใต้สมองเป็นสาเหตุที่พบบ่อยที่สุด (ร้อยละ 40.2) ตามด้วยภาวะโปรแลกตินสูงที่ไม่ทราบสาเหตุ (ร้อยละ 37.1) ร้อยละ 74.3 ของเนื้องอกต่อมใต้สมอง เป็นชนิดไมโครอะดิโนมา ค่ามัธยฐานของขนาดก้อนเนื้องอกเท่ากับ 9 มิลลิเมตร ผู้ป่วย 79 ราย (ร้อยละ 88.8) ได้รับการรักษาด้วยยา ผู้ป่วย 66 ราย ได้รับยาโบรโมคริบตีน ค่าเฉลี่ยของขนาดยาสูงสุดเท่ากับ 5.8 มิลลิกรัม ค่ามัธยฐานของระยะเวลารักษาเท่ากับ 35.8 เดือน พบผลข้างเคียง ร้อยละ 24.2 อาการเวียนศีรษะเป็นอาการข้างเคียงที่พบบ่อยที่สุด ค่ามัธยฐานของเวลาที่ระดับโปรแลกตินกลับมาปกติเท่ากับ 3.8 เดือน ผู้ป่วย 29 ราย ต้องการตั้งครรภ์ มีผู้ป่วย 8 ราย ที่ตั้งครรภ์ ค่ามัธยฐานของเวลาตั้งแต่รักษาจนตั้งครรภ์เท่ากับ 25.9 เดือน ผู้ป่วยที่เป็นแมคโครอะดิโนมามีระดับโปรแลกตินสูงกว่าผู้ป่วยที่เป็นไมโครอะดิโนมาอย่างมีนัยสำคัญทางสถิติ ($p = 0.024$) ผู้ป่วยที่มีอาการน้ำนมไหลจะมาพบแพทย์เร็วที่สุด ($p = 0.010$) ไม่พบความแตกต่างในแง่ของอาการ ระยะเวลาที่มีอาการ ระดับโปรแลกติน ระหว่างผู้ป่วยที่มีและไม่มีเนื้องอกต่อมใต้สมอง ผู้ป่วยที่มีเนื้องอกต่อมใต้สมองต้องการยาที่ขนาดสูงกว่า ($p = 0.009$) และใช้ระยะเวลาในการรักษานานกว่า ($p = 0.007$) ผู้ป่วยที่ไม่มีเนื้องอกต่อมใต้สมอง อัตราการกลับสู่ระดับปกติของโปรแลกตินและการกลับเป็นซ้ำไม่มีความแตกต่างกันระหว่างทั้งสองกลุ่ม ($p = 0.056$ และ 0.374 ตามลำดับ) เวลาในการกลับสู่ระดับปกติของโปรแลกตินและการกลับเป็นซ้ำไม่มีความแตกต่างกันระหว่างผู้ป่วยที่มีและไม่มีเนื้องอก ($p = 0.136$ และ 0.146 ตามลำดับ)*

สรุป: *อาการขาดระดูเป็นอาการที่นำผู้ป่วยมาพบแพทย์ที่พบบ่อยที่สุดในผู้ป่วยสตรีไทยที่มีภาวะโปรแลกตินในเลือดสูงที่มารับการตรวจที่หน่วยต่อมไร้ท่อทางนรีเวช โรงพยาบาลศิริราช ตามด้วยอาการน้ำนมไหล เนื้องอกต่อมใต้สมอง เป็นสาเหตุที่พบบ่อยที่สุด ตามด้วยภาวะโปรแลกตินสูงที่ไม่ทราบสาเหตุ ผู้ป่วยที่มีเนื้องอกต่อมใต้สมองต้องการยาที่ขนาดสูงกว่า และใช้ระยะเวลาในการรักษานานกว่าผู้ป่วยที่ไม่มีเนื้องอกต่อมใต้สมอง*