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Association of High Prolactin Level on Postoperative Day 1 and Tumor Invasion with Female Gonadal Dysfunction After Trans-Sphenoidal Surgery of Pituitary Adenomas

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE Xinmei Huang*
BCF Rui Zhang*
BCD Yueyue Wu
B Li Sheng
B Jiong Xu
F Bingbing Zha
ACEG Jun Liu

Department of Endocrinology, The Fifth People's Hospital of Shanghai, Fudan University, Shanghai, P.R. China

* These authors contributed equally to the study

Corresponding Author: Jun Liu, e-mail: liujun@5thhospital.com

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Background: The aim of this study was to evaluate the risk factors of gonadal dysfunction among Chinese women of reproductive age with pituitary adenomas (PAs) after trans-sphenoidal surgery.

Material/Methods: We retrospectively evaluated 317 women (16–44 years old) who underwent gonadal function and hormone testing before and after trans-sphenoidal surgery for PAs during 2003–2012. Gonadal function was assessed on the basis of menstrual status.

Results: Three women were excluded because of pre-existing gynecological diseases. Before trans-sphenoidal surgery, 34 (10.7%) women were eugonadal and 283 (89.3%) women had gonadal dysfunction. After trans-sphenoidal surgery, 130/189 (68.7%) women with follow-up menstruation data were eugonadal, and 59/189 (31.2%) women exhibited gonadal dysfunction. In addition, 67.4% women of reproductive age with PAs and gonadal dysfunction were restored by trans-sphenoidal surgery ($P<0.01$). Postoperative gonadal dysfunction was independently associated with high prolactin level at day 1 after trans-sphenoidal surgery (odds ratio (OR)=1.024; 95% confidence interval (CI)=1.005–1.043; $P=0.012$) and tumor invasion ($OR=5.752$; $95\%CI=1.618–20.447$; $P<0.01$). Based on the receiver operating characteristic (ROC) curve, prediction of gonadal dysfunction in women of reproductive age after trans-sphenoidal surgery for PAs using prolactin >46.82 µg/L on postoperative day 1 had sensitivity of 88%, specificity of 95%, positive predictive value of 98%, and negative predictive value of 76%, and an area under the ROC curve of 0.701.

Conclusions: Gonadal dysfunction is very common in Chinese women of reproductive age with PAs and can be effectively restored by trans-sphenoidal surgery. Prolactin >46.82 µg/L at 1 day after trans-sphenoidal surgery and tumor invasion can predict postoperative gonadal dysfunction in these patients.

MeSH Keywords: Gonadal Disorders • Pituitary Neoplasms • Risk Factors

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Background

Pituitary adenomas (PAs) are the most common endocrine neoplasms in the hypothalamus-pituitary axis. They account for 5–15% of all intracranial tumors and are the third most frequent tumor type after meningiomas and gliomas in the general population [1,2]. According to the World Health Organization's 2004 classification of pituitary tumors, PAs can be classified into 7 types: prolactinoma, growth hormone (GH)-secreting adenoma, adrenocorticotropin (ACTH)-secreting adenoma, non-functioning adenoma, thyroid-stimulating hormone (TSH)-secreting adenoma, gonadotroph adenoma, and plurihormonal pituitary adenoma [3]. All these PAs are commonly associated with gonadal dysfunction [4–10]. For example, prolactinoma, the most common type of PAs representing approximately 40% of all pituitary tumors [11], is a major cause of gonadal dysfunction. Similarly, gonadal dysfunction is also commonly seen in 50–75% [13,14] of women with acromegaly or GH-secreting adenoma, another relatively common type of PAs with an estimated prevalence of 2.8–13.7 cases/100 000 population or overall prevalence of 54.5% in females [12]. Although studies [7,15–17] have proven that restoration of gonadal function can be achieved by surgery or drugs in women with PAs, its risk factors remain unclear. In the present study, we retrospectively evaluated the effects of trans-sphenoidal surgery in restoring gonadal function and risk factors of gonadal dysfunction among Chinese women of reproductive age with PAs after trans-sphenoidal surgery.

Material and Methods

Patients

This retrospective study was approved by the Ethics Committee of the Shanghai Fifth People's Hospital, Fudan University, and informed consent was obtained from all patients. A total of 1015 patients with PAs were treated and followed-up regularly at our hospital between 2003 and 2012. Of these patients, 317 women with PAs with age at the time of treatment being 16–44 years old who underwent endocrinological evaluation and pituitary imaging were included. Patients were excluded if they had undergone previous surgery, medication or radiotherapy for adenomas, were taking contraceptives, or had been diagnosed with premature ovarian failure, dysplasia of the genital tract, ovarian tumors, or autoimmune thyroid diseases.

The diagnosis of PAs was based on clinical symptoms and signs, including amenorrhea, oligomenorrhea, galactorrhea, infertility, hirsutism, acne, enlargement of the hands and feet, headaches, and vision loss, and was confirmed using data derived from hormone testing, pituitary imaging, and immunohistochemistry of tumor specimens. For our analyses, the following data were collected: 1) age, 2) anthropometric measurements, including body mass index (BMI) in kg/m^2 and galactorrhea, 3) signs or symptoms of gonadal dysfunction, including menstrual disturbances, vaginal dryness, and reduced libido, 4) hormone testing data, 5) pituitary imaging data, and 6) postoperative menstrual status (normal: cycles of 21–35 days; oligomenorrhea: cycles of 35 days to 6 months; or amenorrhea: cycles >6 months).

Pituitary imaging, hormone testing, and pathological diagnosis

Magnetic resonance imaging (MRI) was used to detect and measure PAs and evaluate tumor invasion. Cases of microadenoma, macroadenoma, and giant adenoma were defined as tumors with diameters ≤10 mm, 10–40 mm, and >40 mm, respectively. Invasive PAs were classified as Hardy class III or based upon imaging findings.

Blood testing was performed prior to and 1 day after the surgery to evaluate the serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), testosterone, prolactin (PRL), growth hormone (GH), thyroid-stimulating hormone (TSH), free thyroxine (FT_4), adrenocorticotropic hormone (ACTH), and cortisol. Electrochemiluminescence immunoassays were used to test FSH, LH, E_2, testosterone, and PRL, and chemiluminescence assays were used to test for the remaining hormones. Tumor specimens were fixed in Bouin's solution and embedded in paraffin for pathological testing and immunocytochemistry. Functional PAs were defined as tumors with positive immunohistochemical results for PRL, GH, ACTH, TSH, or gonadotropin.

Diagnosis of gonadal dysfunction

Gonadal function was assessed on the basis of menstrual status. After ruling out menopause, eumenorrhea and normal sex hormone levels were considered to indicate eugonadal condition, while menstrual disorders were considered gonadal dysfunction.

Treatment and follow-up

Of the 317 women included in this study, 291 women underwent trans-sphenoidal resection performed by the same experienced neurosurgeon (Shiqi Li at the Hua Shan Hospital, Fudan University); 12 women underwent craniotomy, 8 women were treated with bromocriptine, 2 women underwent radiotherapy, and 4 women rejected any form of treatment. Data regarding menstrual status after trans-sphenoidal resection were available for 189 women, with follow-up periods ranging from 6 months to 10 years.

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Statistical analysis

Epidata software (*http://epidata.dk*) was used for data entry and SPSS software (version 21.0; SPSS, Inc., Chicago, IL) was used for statistical analysis. Data are presented as medians (interquartile range) or numbers (percentage). Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square tests or Fisher's exact test or McNemar-Bowker test. A logistic regression model was used to analyze the risk factors of gonadal dysfunction after trans-sphenoidal surgery among Chinese women of reproductive age with PAs. Receiver operating characteristic (ROC) curves were used to evaluate the ability of postoperative PRL to predict gonadal dysfunction. All tests were 2-sided and a *P* value <0.05 was considered statistically significant.

Results

Patient baseline characteristics

Of the 317 women with PAs, 128 (40.38%) were age 26–35 years old, 102 (32.18%) were age of 36–44 years old, and 87 (27.44%) were 16–25 years old. All patients underwent MRI to determine tumor size and evaluate tumor invasiveness. The results revealed 105 (33.12%) cases of microadenoma, 210 (66.25%) cases of macroadenoma, 2 (0.63%) cases of giant adenoma, 183 (57.73%) cases of invasive adenoma, and 134 (42.27%) cases of non-invasive adenoma. Prolactinoma was the most common subtype, accounting for (39.1%), followed by PRL- and GH-co-secreting mixed adenoma (8.1%), GH-secreting adenoma (7.5%), non-functioning adenoma (6.9%), ACTH-secreting adenoma (5.9%), and plurihormonal pituitary adenoma (4.4%). In addition, 283 (89.3%) women exhibited preoperative menstrual disorders (the best clinical method for diagnosing gonadal dysfunction) and 34 (10.7%) women had eumenorrhea (indicating eugonadal function). Among patients with menstrual disorders, 161 (56.9%) had amenorrhea and 122 (43.1%) had oligomenorrhea. Compared with eugonadal patients, patients with gonadal dysfunction were younger (*P*<0.01) and exhibited higher PRL level (*P*<0.01) and lower levels of GH (*P*<0.05) and E_2 (*P*<0.01), but no significant differences in tumor invasion, tumor size, BMI, and levels of LH, FSH, testosterone, ACTH, cortisol, TSH, and FT_4 (all *P*>0.05) (Table 1).

Characteristics of patients after trans-sphenoidal surgery

Menstrual status data after trans-sphenoidal surgery were available for 189 women with PAs. Of these 189 women, 130 (68.7%) had eumenorrhea (i.e., eugonadal function) and 59 (31.2%) had menstrual disorders (i.e., gonadal dysfunction). A comparison of gonadal function status before and after trans-sphenoidal surgery revealed that trans-sphenoidal resection was significantly associated with the recovery of normal gonadal function (*P*<0.01, Table 2). As shown in Table 2, compared with patients with postoperative gonadal dysfunction, patients with postoperative eugonadal function had shorter duration of menstrual disorder at baseline (*P*<0.05), lower frequency of invasive pituitary tumors (*P*<0.01), smaller tumor size (*P*<0.05), lower PRL level (*P*<0.01), and higher levels of E_2 (*P*<0.01), testosterone (*P*<0.05), and LH (*P*<0.01) at day 1 after trans-sphenoidal surgery. In addition, patients with postoperative eugonadal function had higher reduction rate of PRL level (P<0.01), and lower reduction rate of E_2 (*P*<0.01) and LH (*P*<0.05) than patients with postoperative gonadal dysfunction. However, there were no significant differences in age, BMI, levels of pituitary hormones (including GH, FSH, ACTH, cortisol, TSH and FT_4) at day one after trans-sphenoidal surgery or reduction rate of hormones (including GH, testosterone, FSH, ACTH, cortisol, TSH and FT_4) at day 1 after trans-sphenoidal surgery.

Risk factors for gonadal dysfunction after trans-sphenoidal surgery

A binary logistic regression analysis was performed to investigate the risk factors of gonadal dysfunction in women of reproductive age with PAs after trans-sphenoidal surgery (Table 3). Model 1 identified that age, tumor invasion, BMI, tumor size, and duration of menstrual disorder were risk factors for gonadal dysfunction, and gonadal dysfunction was independently associated with invasive adenoma [odds ratio *(OR)*=7.680; 95% confidence interval *(CI)*=2.704–21.812; *P*<0.01]. Model 2 included all variables in Model 1 plus hormone levels (PRL, GH, ACTH, cortisol, E_2, testosterone, FSH, LH, TSH, and FT_4) at 1 day after trans-sphenoidal surgery and revealed that gonadal dysfunction was independently associated with higher PRL level at 1 day after trans-sphenoidal surgery (*OR*=1.027; 95%*CI*=1.010–1.044; *P*<0.01) and tumor invasion (*OR*=7.661; 95%*CI*=2.330–25.188; *P*<0.01). Moreover, to adjust for potential confounding factors, Model 3 included the reduction rate of hormone levels at 1 day after trans-sphenoidal surgery besides all variables in Model 2 and found gonadal dysfunction were still independently associated with higher PRL level at 1 day after trans-sphenoidal surgery (*OR*=1.024; *95%CI*=1.005–1.043; *P*=0.012) and tumor invasion (*OR*=5.752; *95%CI*=1.618–20.447; *P*<0.01).

Based on the ROC curve analysis, using PRL level at 1 day after trans-sphenoidal surgery for predicting gonadal dysfunction in women at reproductive age with PAs has an area under the ROC curve of 0.701 (95%*CI*=0.606–0.797) and sensitivity of 88%, specificity of 95%, positive predictive value (PPV) of 98%, and a negative predictive value (NPV) of 76% at the optimal cut-off for PRL level of 46.82 μg/L (Figure 1).

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Table 1. Preoperative clinical and laboratory data according to gonadal function.

Variables	Gonadal dysfunction (n=283)		Eugonadal function (n=34)		*P* values
Tumor invasion					
Invasive	164	(57.95%)	19	(55.88%)	>0.05
Non-invasive	119	(42.04%)	15	(44.12%)	
Tumor size					
Micro (≤10 mm)	96	(33.92%)	9	(26.47%)	>0.05
Macro (10–40 mm)	185	(65.37%)	25	(73.53%)	
Giant (>40 mm)	2	(0.71%)	0	(0)	
Age (years)	30	(25–37)	38	(27.75–41.50)*	<0.001
BMI (kg/m^2)	22.49	(20.32–24.80)	22.60	(20.72–24.76)	>0.05
Pre-PRL (μg/L)	115.60	(45.68–241.30)	30.79	(16.25–63.06)*	<0.001
Pre-GH (μg/L)	0.60	(0.20–1.90)	1.23	(0.41–15.65)**	0.024
Pre-E_2 (pg/mL)	28.48	(15.00–49.64)	41.85	(21.97–100.70)**	0.019
Pre-T (ng/mL)	0.29	(0.15–0.49)	0.20	(0.10–0.42)	>0.05
Pre-LH (IU/L)	3.96	(1.46–6.60)	3.15	(1.28–7.52)	>0.05
Pre-FSH (IU/L)	5.36	(3.74–7.02)	4.61	(3.03–5.73)	>0.05
Pre-ACTH (pg/mL)	27.90	(11.30–35.80)	28.80	(15.70–39.40)	>0.05
Pre-F (nmol/L)	320.16	(155.75–486.32)	390.50	(78.64–555.06)	>0.05
Pre-TSH (mIU/L)	1.33	(0.78–2.20)	1.35	(0.53–2.09)	>0.05
Pre-FT_4 (pg/mL)	1.24	(1.08–1.44)	1.34	(1.13–1.65)	>0.05

BMI – body mass index; Pre-PRL – preoperative prolactin; Pre-GH – preoperative growth hormone; Pre-E_2 – preoperative estradiol; Pre-T – preoperative testosterone; Pre-LH – preoperative luteinizing hormone; Pre-FSH – preoperative follicle-stimulating hormone; Pre-ACTH – preoperative adrenocorticotropin; Pre-F – preoperative cortisol; Pre-TSH – preoperative thyroid-stimulating hormone; Pre-FT_4 – preoperative free thyroxine. Data are presented as median (interquartile range) or number (percentage). Categorical variables were compared using Pearson's Chi-squared test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. * p<0.01, ** p<0.05.

Discussion

Gonadal dysfunction is very common in women of reproductive age with PAs, as shown in our study that 89.3% of premenopausal patients with PAs had gonadal dysfunction as assessed by menstrual disorders, which is a highly valuable technique for diagnosing gonadal dysfunction in women of reproductive age [7,18]. Treatment of patients with PAs with dopamine agonists or surgical approaches can generally restore gonadal function and facilitate conception in >85% of patients with prolactinomas [15]. In addition, gonadal function can be restored by surgery or administration of somatostatin analogs in women with acromegaly [7,16]. In an earlier paper, Caputo et al. reported that surgery restored gonadal axis function in 60% of premenopausal women with non-functional pituitary macroadenomas [17]. Our study also revealed that trans-sphenoidal surgery restored gonadal function in 67.4% of women of reproductive age with PAs. Risk factors of gonadal dysfunction in women of reproductive age with PAs after trans-sphenoidal surgery have been unclear. In the present study, we found that tumor invasion and high PRL level at 1 day after trans-sphenoidal surgery are associated with gonadal dysfunction among Chinese women of reproductive age who underwent trans-sphenoidal surgery for PAs. Moreover, our findings also suggested that PRL >46.82 μg/L at 1 day after trans-sphenoidal surgery can predict gonadal dysfunction.

The relationship between tumor invasion and gonadal dysfunction may involve invasion and destruction of tumor cells into gonadotrophic pituitary cells, which would affect the synthesis

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Table 2. Postoperative clinical and laboratory data according to gonadal function.

Variables	Gonadal dysfunction (n=59)		Eugonadal function (n=130)		*P* values
Gonadal status at baseline					
Gonadal dysfunction	57	(96.61%)	118	(90.77%)*	<0.001
Eugonadal function	2	(3.39%)	12	(9.23%)	
Duration of menstrual disorder (years)					
≤0.5	10	(17.54%)	30	(22.88%)**	
0.5–1	21	(35.09%)	66	(50.85%)	0.017
1–5	20	(33.33%)	30	(22.88%)	
>5	8	(14.04%)	4	(3.39%)	
Tumor invasion					
Invasive	48	(81.25%)	61	(47.06%)*	<0.001
Non-invasive	11	(18.75%)	69	(52.94%)	
Tumor size					
Micro (<10 mm)	12	(20.83%)	52	(40.20%)**	0.015
Macro (10–40 mm)	46	(77.08%)	78	(59.80%)	
Giant (>40 mm)	1	(2.09%)	0	(0)	
Age (years)	31	(26–37)	30	(25–38)	>0.05
BMI (kg/m^2)	23.31	(20.43–25.63)	22.48	(20.28–24.65)	>0.05
Post-PRL-1 (μg/L)	19.75	(5.27–90.34)	9.88	(3.33–20.05)*	<0.001
Post-GH-1 (μg/L)	0.95	(0.60–2.47)	1.30	(0.60–2.75)	>0.05
Post-E_2-1 (pg/mL)	23.20	(10.88–37.55)	34.71	(21.53–69.47)*	0.001
Post-T-1 (ng/mL)	0.25	(0.10–0.45)	0.31	(0.19–0.57)**	0.021
Post-LH-1 (IU/L)	2.40	(0.62–4.49)	2.83	(1.34–5.80)*	0.007
Post-FSH-1 (IU/L)	4.47	(2.87–6.12)	4.90	(3.07–7.11)	>0.05
Post-ACTH-1 (pg/mL)	21.70	(9.92–33.50)	18.50	(9.61–36.55)	>0.05
Post-F-1 (nmol/L)	368.00	(156.18–706.83)	438.84	(191.48–642.50)	>0.05
Post-TSH-1 (mIU/L)	0.68	(0.42–1.13)	0.75	(0.46–1.11)	>0.05
Post-FT_4-1 (pg/mL)	1.25	(1.15–1.43)	1.25	(1.15–1.43)	>0.05
ΔPRL rate (%)	65.75	(32.33–81.97)	90.97	(79.49–97.21)*	<0.001
ΔGH rate (%)	–85.94	(–375.00–14.99)	–150.32	(–500.00–6.26)	>0.05
ΔE_2 rate (%)	13.77	(–39.32–51.26)	–16.97	(–90.50–24.56)*	0.006
ΔT rate (%)	0	(–72.25–49.01)	–12.90	(–74.17–26.17)	>0.05
ΔLH rate (%)	16.32	(–32.95–58.28)	–4.62	(–67.74–37.98)**	0.011
ΔFSH rate (%)	6.80	(–23.67–23.68)	2.30	(–30.27–27.07)	>0.05
ΔACTH rate (%)	8.63	(–25.46–29.12)	0	(–32.62–31.90)	>0.05

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Table 2 continued. Postoperative clinical and laboratory data according to gonadal function.

Variables	Gonadal dysfunction (n=59)		Eugonadal function (n=130)		*P* values
ΔF rate (%)	–37.95	(–99.11–28.97)	–34.41	(–200.83–31.11)	>0.05
ΔTSH rate (%)	38.73	(19.37–67.15)	56.43	(21.00–69.30)	>0.05
ΔFT_4 rate (%)	0.85	(–14.50–13.97)	–2.63	(–17.51–9.58)	>0.05

Post-PRL-1 – prolactin level; Post-GH-1 – growth hormone at one day after operation; Post-E_2-1 – estradiol level at one day after operation; Post-T-1 – testosterone level at one day after operation; Post-LH-1 – luteinizing hormone level at one day after operation; Post-FSH-1 – follicle-stimulating hormone level at one day after operation; Post-ACTH-1 – adrenocorticotropin level at one day after operation; Post-F-1 – cortisol level at one day after operation; Post-TSH-1 – thyroid-stimulating hormone level at one day after operation; Post-FT_4-1 – free thyroxine level at one day after operation; ΔPRL rate is calculated as 1-Post-PRL-1/Pre-PRL; ΔGH rate is calculated as 1-Post-GH-1/Pre-GH; ΔE_2 rate is calculated as 1-Post-E_2-1/Pre-E_2; ΔT rate is calculated as 1-Post-T-1/Pre-T; ΔLH rate is calculated as 1-Post-LH-1/Pre-LH; ΔFSH rate is calculated as 1-Post-FSH-1/Pre-FSH; ΔACTH rate is calculated as 1-Post-ACTH-1/Pre-ACTH; ΔF rate is calculated as 1-Post-F-1/Pre-F; ΔTSH rate is calculated as 1-Post-TSH-1/Pre-TSH; ΔFT_4 rate is calculated as 1-Post-FT_4-1/Pre-FT_4; Data are presented as median (interquartile range) or number (percentage). Categorical variables were compared using Pearson's Chi-squared test, Fisher's exact test, or the McNemar-Bowker test. Continuous variables were compared using the Mann-Whitney U test. * p<0.01, ** p<0.05.

Table 3. Logistic regression analysis of risk factors for gonadal dysfunction after trans-sphenoidal surgery.

	Variables	Estimated coefficients	*SE*	*OR*	95% CI	*P* values
Model 1[a]	Tumor invasion*	2.039	0.533	7.680	2.704–21.812	<0.001
Model 2[b]	Tumor invasion*	2.036	0.607	7.661	2.330–25.188	0.001
	Post-PRL-1*	0.027	0.008	1.027	1.010–1.044	0.002
Model 3[c]	Tumor invasion*	1.749	0.647	5.752	1.618–20.447	0.007
	Post-PRL-1**	0.024	0.009	1.024	1.005–1.043	0.012

SE – standard error; OR – odds ratio; CI – confidence interval; Post-PRL-1 – prolactin level at one day after operation; * p<0.01, ** p<0.05. [a] Model 1 was adjusted for age, tumor invasion, body mass index, tumor size, and duration of menstrual abnormality. [b] Model 2 included all variables in Model 1 plus hormone levels level at one day after operation, such as prolactin, growth hormone, adrenocorticotropin, cortisol, estradiol, testosterone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, and free thyroxine. [c] Model 3 included all variables in Model 2 plus reduction rate of hormone levels level at one day after operation, such as prolactin, growth hormone, adrenocorticotropin, cortisol, estradiol, testosterone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, and free thyroxine.

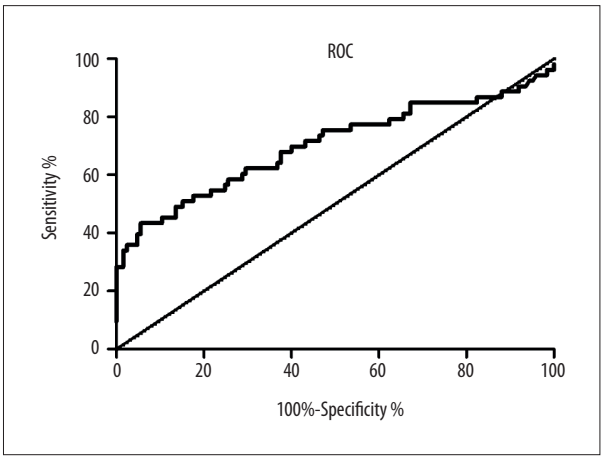

Figure 1. Receiver operating characteristic (ROC) curve of prolactin level at 1 day after trans-sphenoidal surgery for predicting gonadal dysfunction in Chinese women of reproductive age who underwent trans-sphenoidal surgery for pituitary adenomas.

of LH and FSH, and ultimately result in gonadal dysfunction. Hyperprolactinemia has been shown to interrupt hypothalamic production of gonadotropin-releasing hormone, inhibiting the release of LH, FSH, and E_2 [15,19]. In addition, hyperprolactinemia in mice induced hypogonadotropic anovulation, diminished kisspeptin expression, inhibited peripheral kisspeptin administration, and restored GnRH, gonadotropin secretion, and ovarian cyclicity, suggesting that kisspeptin neurons

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play a major role in hyperprolactinemic gonadal disorder [5], consistent with the results showing that chronic prolactin administration suppressed serum LH and reduced Kiss1 mRNA levels in the rostral periventricular region of the third ventricle and arcuate nucleus [20]. Unfortunately, kisspeptin protein expression and Kiss1 mRNA level were not tested in our study. Although few studies have shown that gonadal dysfunction is also correlated with high levels of GH and cortisol as well as abnormal sex hormone binding globulin [5,5,10,11], these factors were not related to the gonadal dysfunction of women of reproductive age who underwent trans-sphenoidal surgery for PAs in our study.

Conclusions

Our study showed that trans-sphenoidal surgery is able to restore normal gonadal function in Chinese women of reproductive age with PAs and tumor invasion and high PRL level at 1 day after trans-sphenoidal surgery are risk factors of gonadal dysfunction of patients who underwent trans-sphenoidal surgery for PAs. In addition, PRL >46.82 μg/L at 1 day after trans-sphenoidal surgery is an indicator for postoperative gonadal dysfunction.

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