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Effect of Surgery on Gonadal Function of Premenopausal Women with Pituitary Adenomas Other Than Prolactinomas

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Abstract. The effects of surgery on pituitary-gonadal function were investigated in women with pituitary adenomas other than prolactinomas. The subjects were 46 women of premenopausal age with a pituitary adenoma. Twenty tumors were GH producing, 19 were nonfunctioning, and 7 were adrenocorticotropin producing adenomas. The surgery was performed mainly via the transsphenoidal route, with the aim of eradicating the tumor and preserving pituitary function. The menstrual cycle was preserved postoperatively in 9 out of 10 (90%) patients with regular preoperative menstruation. Menstrual disturbance was seen in 36 (78.3%) cases preoperatively. The causative factors for menstrual disturbance were gonadotropin impairment and hyperprolactinemia in GH producing and nonfunctioning adenoma. Excessive hormonal secretion itself is a major causative factor for menstrual disturbance in GH and ACTH producing adenoma. Regular menstruation was restored following surgery in 20 out of 36 (55.6%) patients with menstrual problems. The predicting factors for postoperative recovery of menstruation are: size of adenoma less than 40 mm, period of amenorrhea less than 5 years, and preoperatively preserved gonadotropin secretion. In addition, preoperative hyperprolactinemia was also a predicting factor in women with nonfunctioning adenoma. Thus, even in patients with pituitary adenomas other than prolactinoma, the restoration of menstruation is highly achievable when surgery is performed with attention to preserving pituitary function.

Key words: Gonadal function, Menstrual disorders, Pituitary adenoma

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THE PURPOSE of surgery for pituitary adenomas is to eliminate existing symptoms caused by the mass effect or endocrine hyperactivity of a tumor, and if possible to eradicate the tumor itself. In addition, surgery should be directed toward the preservation or restoration of pituitary function, because the patient's life expectancy is usually quite long.

In general, the clinical evaluation of anterior pituitary function is not easy. It is easier in premenopausal women, because their menstrual status directly reflects the efficiency of the hypothalamic-pituitary-gonadal axis. A regular menstrual cycle following surgery is a good indicator of well-preserved or restored anterior pituitary function. There are only a few episodic reports concerning gonadal function in women with pituitary adenomas other than prolactinoma [1–6]. Therefore, we conducted a systematic endocrinological and clinical study of gonadal function in premenopausal women with pituitary adenomas other than prolactinoma, to determine the effect of selective adenomectomy on anterior pituitary function. In addition, factors which influence postoperative pi-

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tuitary gonadal function were investigated.

Subjects

The subjects included 46 women between the ages of 12 and 44 years (mean ± SD; 31.2 ± 8.8) with pituitary adenomas other than prolactinomas, who underwent surgery within the last 15 years at the Department of Neurosurgery, Hiroshima University School of Medicine, and were followed up for more than 6 months following surgery. There were 20 GH producing, 19 nonfunctioning, and seven ACTH producing adenomas. The mean age was 31.1 ± 9.7 for GH producing adenomas, 33.2 ± 7.3 for nonfunctioning adenomas, and 28.1 ± 10.8 for ACTH producing adenomas. The follow-up period ranged from 8 to 168 months (mean: 79.2 ± 48.9 months). The mean diameter of the tumors was 19.0 ± 8.6 mm for GH producing, 29.6 ± 11.9 for nonfunctioning, and 7.1 ± 1.3 for ACTH producing adenomas. Transsphenoidal adenomectomy was the route of surgery in all but 2 cases.

Methods

The transsphenoidal adenomectomies performed in this series were essentially the same as originally described by Hardy [7, 8]. The following precautions, however, were always taken during surgery to avoid mechanical insults to the pituitary tissue or disturbance of the pituitary blood flow: 1) curettage was very gently and carefully done, especially in the direction of pituitary stalk, 2) the suprasellar portion of the adenoma was allowed to descend naturally, and the tumor capsule, pituitary gland, and pituitary stalk were never pulled down, 3) the pituitary tissue was not detached from the surrounding dura mater, 4) the pituitary tissue was resected as little as possible, and 5) a second stage operation was considered when the natural descent of the suprasellar portion did not occur. Gross total removal of the tumor was achieved in 71.7% (33 of 46 cases) by the first operation.

Radiation therapy was usually performed only in patients in whom multi-stage surgery failed to remove the major part of the adenoma. In 4 patients with nonfunctioning pituitary adenomas, it was administered with a linear accelerator to a total dose of 50 Gy.

Menstruation was defined as normal when it appeared every 25 to 38 days. Oligomenorrhea was defined as less than nine menses a year. Amenorrhea was defined as no menstruation for the last 6 months.

The function of the anterior pituitary was systematically evaluated before and after surgery (between 3 months and 12 months after surgery) by three types of provocative tests—the insulin tolerance test (ITT), the thyrotropin releasing hormone (TRH) test, and the luteinizing hormone releasing hormone (LH-RH) test. All six anterior pituitary hormones were measured by specific radioimmunoassays (RIA) or immunoradiometric assays (IRMA) in which levels were converted into the levels measured by the RIA method. The evaluation of anterior pituitary function was based on the criteria [9] proposed by one of the senior authors, based on the menstrual history of Japanese women (Table 1). Here "post-operative" values represent the hormonal values obtained following the end of the last operation and prior to radiation therapy.

Statistical significance was assessed by means of the Chi-square test; a P value of less than 0.05 was considered statistically significant.

Results

GH producing adenoma

Prior to surgery, menstrual disorders existed in 16 patients (80%), (primary amenorrhea in 1, secondary amenorrhea in 9, and oligomenorrhea in 6) (Table 2). Four of the 16 patients with menstrual disorders had hyperprolactinemia and gonadotro-

Table 1. Criteria for normal range in provocative tests for premenopausal woman

		base	peak
GH	ng/m*l*	< 5	> 10
cortisol	μg/dl	4–18	> 16
TSH	μU/m*l*	< 10	> 8
PRL	ng/ml	< 25	> 15
LH	mIU/m*l*	< 36	> 30
FSH	mIU/m*l*	< 22	> 5

The values measured by the IRMA were convereted into the values measured by the RIA method.

Table 2. GH producing pituitary adenomas presented with menstrual disturbance (n=16)

Status of menstruation			PRL	LH	FSH	GH	Wished	Became
pre	post	case	pre → post	pre → post	pre → post	post	for child	pregnant
amenorrehea	regular	1	H → H#	L → N	N → N	N	+	+
10 cases	5 cases	2	N → N	N → N	N → N	N	–	–
		3	N → N	L → L	N → N	N	–	–
		4	N → N	N → N	N → N	H#	–	–
		5	N → N	N → L	N → N	N	+	–
	amenorrhea	6	H → L	N → L	N → N	N	+	–
	5 cases	7	N → N	L → L	N → L	N	–	–
		8	H → H#	L → L	L → L	N	–	–
		9	H → H#	L → L	N → N	H#	–	–
		10	N → N	N → N	N → N	N	–	–
oligomenorrhea	regular	11	N → N	L → L	N → N	N	+	+
6 cases	5 cases	12	N → N	N → N	N → N	N	–	+
		13	N → N	N → N	N → N	H#	–	–
		14	N → N	N → N	N → N	N	–	–
		15	H → N	L → L	N → L	N	–	–
	oligomenorrhea							
	1 case	16	n.m.→ N	N → N	N → N	N	–	+

N, normal; H, high; H#, lowered but still high; L, low; n.m., not measured; pre, preoperation; post, postoperation.

pin deficiency, 1 patient had hyperprolactinemia only, and 3 patients had gonadotropin deficiency alone. Seven patients had none of these abnormalities. A normal menstrual cycle returned postoperatively in 10 patients (62.5%) (5 with amenorrhea, and 5 with oligomenorrhea). In 7 of these 10 patients, hyperprolactinemia was not present, and gonadotropin secretion was not changed by the surgery. Among the 4 patients with normal menstruation, one who had undergone a previous transcranial operation at another hospital, became amenorrheic following transsphenoidal surgery.

Nonfunctioning adenoma

All the "nonfunctioning" adenomas were verified histologically as not being prolactinomas by immunostaining when they were accompanied by mild hyperprolactinemia

Prior to surgery, menstrual disorders existed in 15 patients (78.9%) (secondary amenorrhea in 14, and oligomenorrhea in 1) (Table 3). Three of these patients had hyperprolactinemia and gonadotropin deficiency, 6 had hyperprolactinemia only, and 5 had gonadotropin deficiency only. One patient had neither deficiency. A normal menstrual cycle was restored postoperatively in 7 (46.7%) patients (6 with secondary amenorrhea and 1 with oligomenorrhea). Gonadotropin secretion returned to normal in 2 of these 7 patients postoperatively. Six patients with restored menses had high blood PRL concentrations preoperatively. Four of these 6 patients had normal PRL concentrations postoperatively. All 4 patients with regular menstrual cycles preoperatively maintained them postoperatively.

ACTH producing adenoma

Before surgery menstrual disorders existed in 5 patients (71.4%) (secondary amenorrhea in 3 and oligomenorrhea in 2) (Table 4). Two of these 5 patients had gonadotropin deficiencies. No patient had hyperprolactinemia. Normal menstruation was restored postoperatively in 3 (60%) patients, who were all amenorrheal preoperatively. Gonadotropin secretion normalized postoperatively in 1 of these 3 patients.

Both patients with regular menstrual cycles preoperatively maintained them postoperatively.

Pregnancy following surgery

Prior to surgery 10 patients (4 with GH producing and 6 with nonfunctioning adenomas) wished for a baby. Two patients with GH producing ade-

Table 3. Nonfunctioning pituitary adenomas presented with menstrual disturbance (n=15)

Status of menstruation			PRL	LH	FSH	Wished	Became
pre	post	case	pre → post	pre → post	pre → post	for child	pregnant
amenorrehea	regular	1	H → N	N → N	N → N	–	–
14 cases	6 cases	2	N → N	N → N	N → N	+	+
		3	H → H	N → N	N → N	–	–
		4	H → N	N → N	N → N	–	–
		5	H → N	N → N	N → N	–	–
		6	H → N	L → N	N → N	–	–
	oligomenorrhea						
	1 case	7	N → N	L → L	L → N	+	+
	amenorrhea	8	H → N	L → L	N → N	–	–
	7 cases	9	H → N	N → L	N → N	–	–
		10	N → N	L → L	L → N	+	–
		11	H → N	N → N	N → N	–	–
		12	N → N	L → L	N → L	–	–
		13	N → N	L → L	N → N	–	–
		14	N → N	L → L	N → L	–	–
oligomenorrhea	regular						
1 case	1 case	15	H → N	L → N	N → N	–	+

N, normal; H, high; L, low; pre, preoperation; post, postoperation.

Table 4. ACTH producing pituitary adenomas presented with menstrual disturbance (n=5)

Status of menstruction			Result of	LH	FSH	Wished	Became
pre	post	case	surgery	pre → post	pre → post	for child	pregnant
amenorrehea	regular	1	cure	N → N	N → N	–	–
3 cases	3 cases	2	remit	N → N	N → N	–	–
		3	remit	L → N	N → N	–	–
oligomenorrhea	oligomenorrhea	4	cure	N → L	N → L	–	–
2 cases	2 cases	5	improved	L → L	N → N	–	–

N, normal; L, low; pre, preoperation; post, postoperation.

nomas, including 1 amenorrheic patient, and 2 patients with nonfunctioning adenomas, including 1 amenorrhic patient, conceived naturally following surgery (Tables 2, 3).

Factor causing preoperative menstrual disorders (Fig. 1)

As a factor causing menstrual disturbance, gonadotropin deficiency was seen preoperatively in 40% to 53.3% of patients. And hyperprolactinemia was seen in 31.7% of patients with GH producing and in 60% of those with nonfunctioning adenoma. Neither kind of abnormality, however, was seen in 43.8% of GH and 60% of ACTH producing adenoma.

Factors indicating postoperative recovery of normal menstruation

The possibility of recovery of normal menstruation was significantly higher in cases with a tumor less than 40 mm (P=0.005) and with duration of amenorrhea longer than 5 years (P=0.036). The 8 patients with a tumor larger than 40 mm in diameter or with amenorrhea lasting more than 5 years never regained the menstrual cycle (Fig. 2). Among the other 18 patients with secondary amenorrhea, the incidence of spontaneous restoration of regular menstruation was high (77.8%).

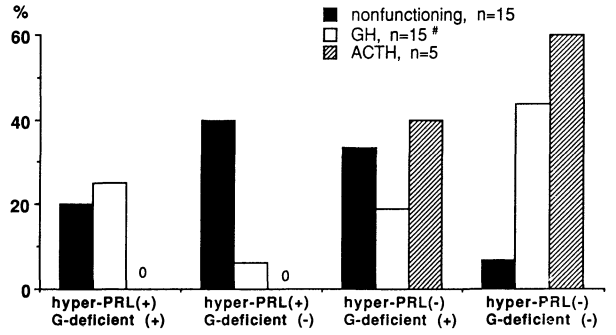

Fig. 1. Preoperative status of prolactin and gonadotropin secretion in women with menstrual disturbance. #: excluding one in which the prolactin level was not measured. hyper-PRL, hyperprolactinemia; G-deficient, gonadotropin deficiency. A considerable proportion of women with GH (43.8%) and ACTH (60%) producing adenoma did not show hyperprolactinemia nor gonadotropin deficiency.

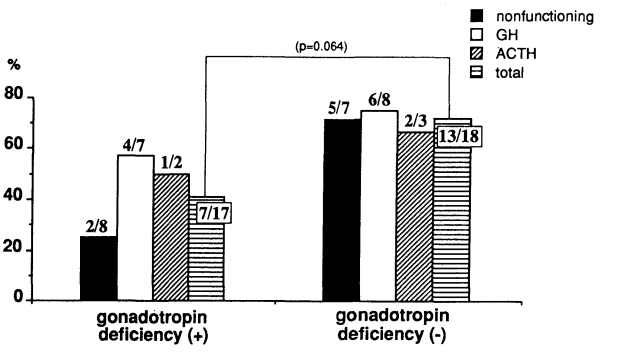

Fig. 3. Difference between women with and without preoperative gonadotropin deficiency in incidence of postoperative normalization. The denominator is the number of women with preoperative menstrual disturbance. The numerator is the number of women who had normal menstruation restored. Overall women with preserved gonadotropin secretion tended to recover regular menstrual cycles postoperatively.

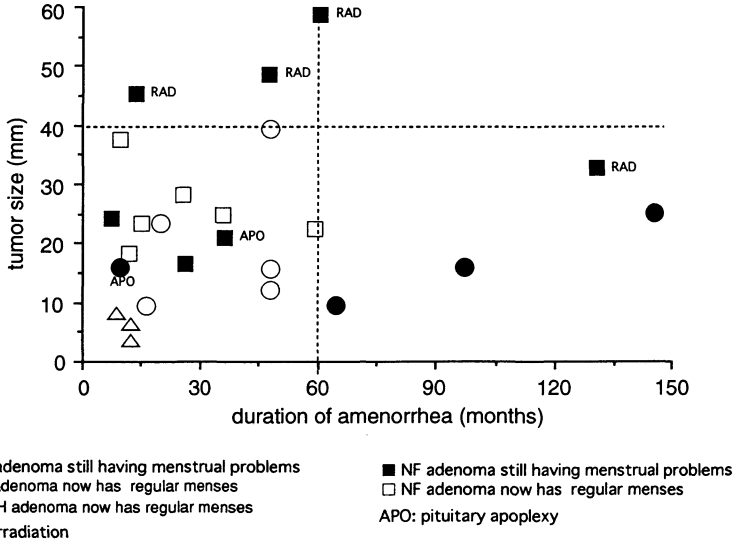

Fig. 2. Correlation of postoperative menstrual status with tumor size and preoperative duration of amenorrhea. When the tumor size was smaller than 40 mm and the duration of amenorrhea was shorter than 5 years, postoperative restoration of menstruation occurred frequently.

There was a positive relation, although not statistically significant (P=0.064), between preoperative preservation of gonadotropin secretion and postoperative recovery of normal menstruation (Fig. 3). And cases with nonfunctioning adenoma accompanied by hyperprolactinemia tend to recover their menstrual cycles postoperatively (P=0.057) (Fig. 4). The normalization of menstruation was achieved in 6 out of 9 patients with hyperprolactinemia, but in only 1 out of 6 patients without it (Table 3).

Function of anterior pituitary hormones

The surgery rarely impaired the function of anterior pituitary function. The total deficiency ratio

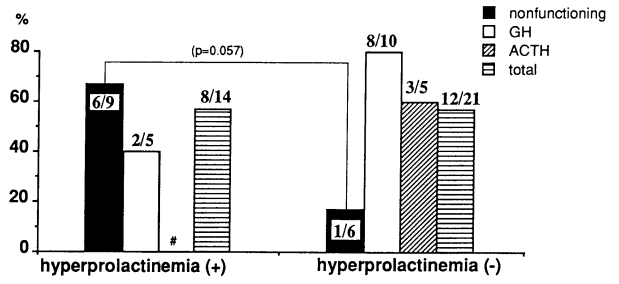

Fig. 4. Difference between women with and without hyperprolactinemia in incidence of postoperative normalization. #: There was no ACTH adenoma with hyperprolactinemia. The denominator is the number of women with preoperative menstrual disturbance. The numerator is the number of women who had normal menstruation restored. Women with nonfunctioning adenoma accompanied by hyperprolactinemia tend to recover the normal menstrual cycle after surgery.

in the secretion of all six anterior pituitary hormones was 35.8% preoperatively and 39.3% postoperatively (data not shown). Postoperative chronic replacement of cortisol, with or without thyroid hormone, was started in 4 patients. Two of these 4 patients underwent radiation therapy following surgery. In the remaining 2 patients, surgery appeared to be causative of the postoperative hypopituitarism.

Discussion

Function oriented pituitary surgery

Recently, it has been demonstrated that chronic systemic estrogen deficiency causes several serious health problems in postmenopausal women, and gonadal steroid replacement therapy is now common [10–15]. It is therefore important to preserve or restore pituitary gonadal function in women with pituitary adenomas because it will be of benefit to the long-term quality of life, as well as in restoring fertility. We adhere to the concept of "function oriented pituitary surgery" preserving anterior pituitary function as much as possible in the surgical treatment of pituitary adenoma. In our previously reported series of 47 cases of microprolactinoma, transsphenoidal surgery performed with the precautions mentioned above provided a high rate (71%) of postoperative restoration of menstruation [16]. In addition, 76% of 67 infertile patients with prolactinomas became pregnant following surgery [17]. These results demonstrated well-preserved anterior pituitary function, as well as a sufficient decrease in the PRL level.

As is well known, the goal of surgical treatment is tailored to the kind of hormones that an adenomas is producing. For example, an ACTH producing pituitary adenoma should be eradicated at the price of pituitary function, because of the tragic natural course of Cushing's disease. But even in such cases the authors have performed initial surgical intervention giving high consideration to preserving pituitary function.

Of the 46 current cases, 10 patients had regular menstrual cycles preoperatively. Only 1 patient became amenorrheic postoperatively. In that case, as postoperative gonadotropin secretion was normal, the surgical intervention might not have been responsible for her loss of menstruation. Nevertheless, the rate of preservation of a regular menstrual cycle was very high (90%).

Thirty-six patients (78%) had menstrual disturbance prior to surgery. Regular menstruation was restored in 20 patients (57.1%) following surgery. There are very few reports [2, 4, 5, 18] on the postoperative improvement in gonadal function in patients with pituitary adenomas other than prolactinoma. Erlichman has reported that 29 of 44 women with nonfunctioning pituitary adenomas were amenorrheic, and 7 (24.1%) of the 29 patients, including two women who became pregnant, had restoration of menstruation following surgery [4]. Arafha has reported that 25 of 26 patients with nonfunctioning pituitary adenomas had hypogonadism, which improved in 8 (32.0%) [2]. The rate of improvement in pituitary-gonadal function in our report is much better than in these series. Function oriented pituitary surgery, and the avoidance of premature irradiation [19–21] seem to be the main factors which provided better results in our series.

Factors causing preoperative menstrual disorders

In 16 patients with nonfunctioning adenomas with preoperative menstrual disorders, the majority had hyperprolactinemia, gonadotropin deficiency, or both. Hyperprolactinemia, gonadotropin deficiency, or both are therefore overwhelming causes of gonadal dysfunction in

patients with nonfunctioning pituitary adenomas [2, 4].

In 16 patients with GH producing adenomas and preoperative menstrual problems, gonadotropin deficiency and hyperprolactinemia also were observed [22, 23] but a considerable portion of the patients (43.8%) did not have gonadotropin deficiencies or hyperprolactinemia. In addition, in 2 patients with preoperative menstrual disorders and gonadotropin deficiency but without hyperprolactinemia, the restoration of regular menstruation was accompanied by normalization of GH secretion, but not by recovery of gonadotropin secretion. The high blood GH concentration itself therefore seems to be the causative factor in gonadal dysfunction in these patients with GH secreting pituitary adenomas. Some acromegalic patients with galactorrhea do not have increased prolactin [24]. In addition GH is known to be a prolactin agonist [25, 26]. Our results suggest that excessive GH disturbs the hypothalamic-pituitary-gonadal axis, probably due to an the excessive PRL-like effect.

Three of 5 patients with ACTH producing adenomas and gonadal dysfunction had normal gonadotropin secretion. Two out of these 3 patients recovered their menstrual cycles as the hypercortisolism improved. As is well known, this re-confirmed that hypercortisolism itself disturbs the hypothalamic-pituitary-gonadal axis in Cushing's disease [27–31].

Factors predicting restoration of menstruation

Our data clearly show that there is no chance of restoring menstruation when the adenoma is more than 40 mm in diameter, or the amenorrhea has lasted for more than 5 years, seemingly enough time to lead to secondary gonadal atrophy. On the other hand, when the tumor is less than 40 mm in diameter and the duration of amenorrhea is shorter than 5 years, the possibility of the postoperative restoration of menstruation is very high. Postoperative normalization of menstruation was also highly achievable (72.2%, 13 out of 18 cases) in the patients whose preoperative gonadotropin secretion was well preserved.

In patients with nonfunctioning adenomas, preoperative hyperprolactinemia was another factor predicting postoperative normalization of the menstrual cycle. This suggests that, in these cases, the pituitary-gonadal dysfunction is not caused by direct damage to pituitary tissue, but rather by compression on the pituitary portal system [2]. This dysfunction is relatively easy to recover by selective adenomectomy.

The restoration of menstruation should therefore not be compromised by excessive and reckless manipulation of the pituitary gland, especially in patients with the good predicting factors mentioned here.

Conclusion

In premenopausal women with pituitary adenomas other than prolactinomas, function oriented selective adenomectomy rarely damages anterior pituitary function and achieves a high rate of preservation and restoration of gonadal function.

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