

Diagnosis of pituitary gonadotroph adenomas in reproductive-aged women

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Objective: To describe the clinical symptoms associated with the diagnosis of pituitary gonadotroph adenoma in premenopausal women.

Design: Report of three separate cases.

Setting: University medical center.

Patient(s): Three patients: a 31-year-old woman with primary infertility, recurrent adnexal masses, and highly elevated estradiol level; a 30-year-old woman with recurrent multicystic ovaries following multiple cystectomies and transvaginal cyst aspirations, and elevated estradiol level; a 43-year-old woman with bilateral complex cystic adnexal masses and an elevated estradiol level, who underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy for a suspected granulosa cell tumor.

Intervention(s): Transsphenoidal resection of a pituitary mass.

Main Outcome Measure(s): Serum estradiol, FSH, and LH levels; transvaginal ultrasonography of the ovaries; histologic examination of pituitary tumors.

Result(s): Transsphenoidal resection of pituitary adenomas resulted in normalization of serum estradiol and FSH levels and resolution of adnexal masses in two of the women.

Conclusion(s): Pituitary gonadotroph adenoma must be considered in the differential diagnosis in reproductive-aged women presenting with the clinical symptom triad of new onset oligomenorrhea, bilateral cystic adnexal masses, and elevated estradiol and FSH levels with suppressed levels of LH; timely diagnosis may prevent unnecessary and potentially damaging surgical procedures. (Fertil Steril® 2005;84:757.e1–6. ©2005 by American Society for Reproductive Medicine.)

Key Words: Gonadotroph adenoma, estradiol, FSH, LH, ovarian hyperstimulation

Gonadotroph adenomas are pituitary tumors that originate from the gonadotroph cells of the pituitary gland. They are not uncommon, accounting for up to 40% of all clinically recognized pituitary macroadenomas (1, 2). Gonadotroph adenomas can secrete intact FSH, LH, and their subunits. However, the hormone secretion is inefficient and frequently fails to produce clinical signs and symptoms (1). When symptoms do exist, most result from the sellar mass effect of the macroadenoma, and include headache and compromised visual fields (3). In postmenopausal women, other symptoms are rare, as ovarian failure precludes ovarian stimulation due to elevated gonadotropins (2). In contrast, premenopausal women with FSH-secreting adenomas may present with ovarian hyperstimulation. However, this presentation appears to be rare and has previously been described only in isolated case reports (4–10).

We present three cases of FSH-secreting adenomas in premenopausal women who presented with menstrual disturbances, ovarian hyperstimulation, and aberrant pituitary

and ovarian hormonal profiles. Our intent is to describe the clinical presentation, find common characteristics, and propose a constellation of signs and symptoms that will suggest this diagnosis.

CASE REPORTS

Patient 1

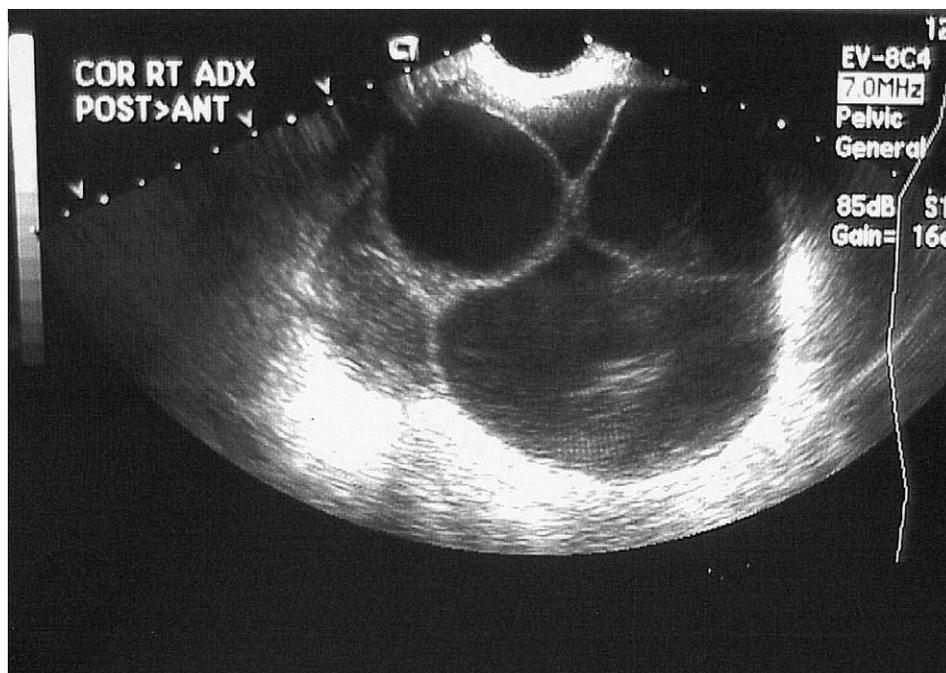
A 31-year-old nulligravid woman presented to the endocrine/infertility clinic complaining of an inability to conceive for 4 years. She had undergone an exploratory laparotomy and bilateral ovarian cystectomy 5 years before presentation, which was followed by a laparoscopic bilateral ovarian cystectomy 2 years later for recurrent benign ovarian cysts. She received 2 months of depo-leuprolide acetate injections following the second surgery, which failed to suppress cyst growth. The patient experienced menarche at 15 years of age. Menses were regular at first, but had become irregular with menstrual intervals of 1 to 2 months over the past several years. She had no other significant medical history and denied use of any medications. On physical examination the patient weighed 70 kg and was 167 cm tall. She was a well-developed female with no gross physical abnormalities. Visual field examination was normal. Pelvic examination revealed bilateral adnexal masses.

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FIGURE 1

Transvaginal ultrasound of the ovary of a 31-year-old woman with a follicle-stimulating hormone–secreting pituitary microadenoma.



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Transvaginal ultrasonography revealed a $9.1 \times 4.9 \times 5.1$ cm uterus with a 7-mm endometrial echo complex (EEC), a $7.4 \times 7.9 \times 5.0$ cm right ovary with multiple cysts 15 to 45 mm in size, and a $8.5 \times 4.6 \times 6.7$ cm left ovary containing multiple cysts 20 to 40 mm in size (Fig. 1).

Initial laboratory tests revealed an estradiol level of 2,436 pg/mL, an FSH level of 14 mIU/mL, and an LH level of < 1.0 mIU/mL (Table 1). The prolactin level was 24.6 ng/mL. The TSH level was $1.5 \mu\text{IU/mL}$. Four weeks later, the estradiol level rose to 3,944 pg/mL while FSH remained at 14 mIU/mL and LH was still undetectable (< 1.0 mIU/mL). An inhibin A level was measured at 294 pg/mL (normal: < 98 pg/mL). The progesterone level returned 2.0 ng/mL, and the total testosterone level was 51 ng/dL. Persistence of the adnexal masses, and elevated estradiol and FSH levels prompted magnetic resonance imaging (MRI) of the pituitary, which revealed a 0.9-cm microadenoma.

The patient underwent transsphenoidal resection of a discrete pituitary mass without complications. The remaining gland was left intact. Immunohistochemical studies of the tumor for anterior pituitary hormones revealed focal diffuse cytoplasmic staining for FSH, while none was detected for LH, prolactin, GH, ACTH, or TSH. Four weeks after surgery, the patient was asymptomatic and a repeat transvaginal ultrasonography revealed a normal size uterus with a 10-mm EEC. The right ovary measured $5.0 \times 3.6 \times 3.0$ cm and had

a single 17 mm follicle, while the left ovary measured $3.5 \times 3.4 \times 2.7$ cm and appeared normal. Laboratory tests revealed normalization of estradiol, FSH, and LH levels (see Table 1).

Patient 2

A 30-year-old nulliparous woman presented to her gynecologist complaining of amenorrhea and inability to conceive following discontinuation of oral contraceptive pills (OCs) 2 years before. She had no significant medical history, and did not use any other medication. The patient was diagnosed with bilaterally enlarged cystic ovaries and underwent an emergent laparotomy and bilateral ovarian cystectomy. Subsequently, the patient was placed on a trial of OCs and 2 months of leuprolide acetate. When she presented to a second gynecologist, the patient complained of significant pelvic pain, and difficulty with breathing and exercising. On physical examination, the patient weighed 55 kg and was 163 cm tall. She appeared as a normally developed female. Her pelvic examination revealed a mildly tender abdominal/pelvic mass reaching the level of the umbilicus.

Transvaginal ultrasonography revealed a normal size uterus with a thin EEC, a $16 \times 9.5 \times 8$ cm right ovary with more than 30 simple cysts of various sizes, a $13 \times 11 \times 6.4$ cm left ovary with multiple cysts, and a small amount of free cul-de-sac fluid. Initial laboratory tests revealed an estradiol level > 500 pg/mL (above assay limit), an FSH level of 22

TABLE 1**Hormone levels in three patients with gonadotroph adenomas.**

Hormone level	Patient 1		Patient 2		Patient 3		
	Basal	After transsphenoidal resection	Basal	After transsphenoidal resection	Basal	After TAH/BSO	After transsphenoidal resection
Estradiol (pg/mL)	952–3,944	130	500–1,420	50	676	114, 62	—
Inhibin A (pg/mL)	213–294	—	—	—	529–617	<10	—
FSH (mIU/mL)	11–14	5.1	14–18	2–6	—	56	—
LH (mIU/mL)	<1.0	2.2	<1.0–2.0	<1.0	—	1.1	—
Prolactin (ng/mL)	22–46	5.6	58	39–42	—	64	—
Testosterone (ng/dL)	48–57	35	69–144	<10–54	—	—	—

Note: BSO = bilateral salpingo-oophorectomy; TAH = total abdominal hysterectomy.

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mIU/mL, and an LH level of 1.0 mIU/mL. Prolactin was elevated at 58 ng/mL, while the TSH level was 2.7 μ IU/mL.

The patient was placed on OCs and underwent transvaginal aspiration of the cysts, resulting in recovery of approximately 1 liter of serous fluid. This resulted in some relief of the patient's symptoms. Although the ovarian volume was reduced, the ovaries remained multicystic and enlarged. The patient received a third injection of leuprolide acetate, which did not resolve the cystic ovaries. Repeat laboratory tests revealed an estradiol level >500 pg/mL, an FSH level of 14 mIU/mL, and an LH level of 1.1 mIU/mL.

Over the course of the next 4 weeks, the patient underwent two additional transvaginal cyst aspirations with recovery of approximately 1 liter of fluid on each occasion. As the cysts continued to recur, a second laparotomy was undertaken in which multiple bilateral ovarian cystectomies was performed. Dense pelvic adhesions were noted at the time of laparotomy. Final pathology on the resected cysts revealed multiple cystic follicles. When the cysts recurred once again, a laparoscopic cystectomy was performed with similar results.

Six months after initial presentation, an MRI study of the pituitary was performed revealing a 17 \times 16 mm pituitary macroadenoma. The patient underwent transsphenoidal resection of a well-defined pituitary mass, and had a normal postoperative course. Within 1 week of pituitary surgery, the patient's hormonal profile returned to normal (see Table 1). She resumed normal menses and has since conceived spontaneously and delivered a healthy child.

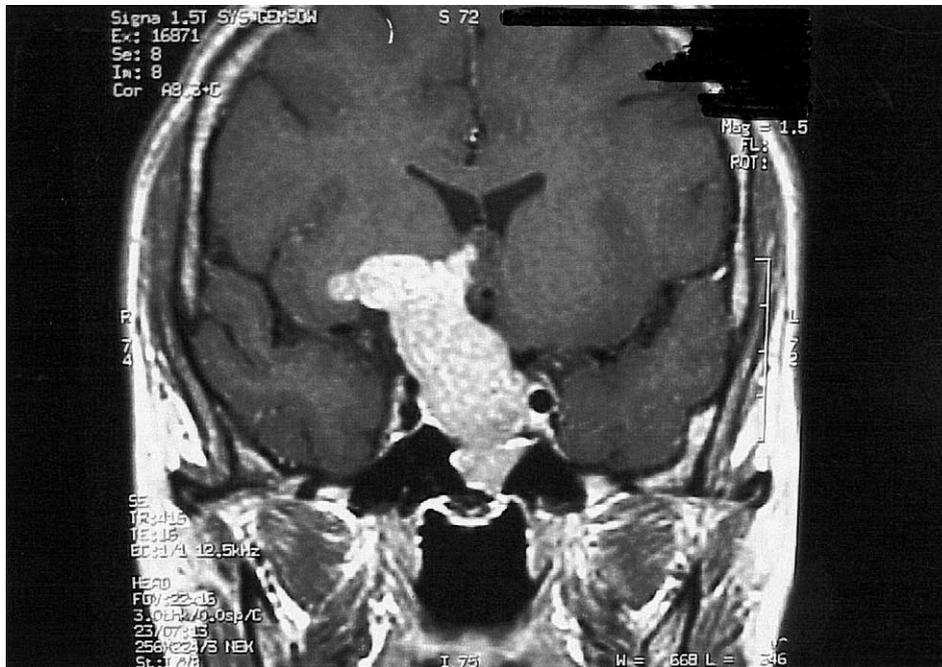
Patient 3

A 43-year-old gravida 7, para 7 woman was referred to the gynecologic oncology clinic from an outside center for bilateral adnexal masses. The patient was without complaints except for a slight increase in abdominal girth over the course of the preceding year. The patient had no significant medical or surgical history, and she denied use of any medication or weight loss. She reported menarche at 16 years of age with regular monthly menses until 39 years of age, at which time menses became irregular, occurring every 2 to 4 months. Her obstetric history was significant for seven term spontaneous vaginal deliveries. On physical examination, the patient weighed 53 kg and was 147 cm tall. She appeared as a normally developed female. Her pelvic examination revealed bilateral adnexal masses. Transvaginal ultrasonography revealed a 13.2 \times 8.3 \times 7.0 cm uterus with an 8-mm EEC, a 9.7 \times 6.6 \times 6.3 complex cystic left adnexal mass, an 8.2 \times 7.5 \times 6.7 cm complex cystic right adnexal mass, and a small amount of free cul-de-sac fluid.

Initial laboratory tests revealed a normal CA-125 tumor marker level. The estradiol level was 676 pg/mL. The inhibin A level as 529 pg/mL (normal: <98 pg/mL), and a repeat level was 617 pg/mL. Because of concerns for a granulosa cell tumor (GCT) of the ovaries, an exploratory laparotomy was performed, which included a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Intraoperative findings included approximately 50 mL of pelvic fluid, an enlarged uterus with evidence of adenomyosis, and bilaterally enlarged multicystic ovaries (6 to 8 cm), which, on a rapid frozen section pathologic exam-

FIGURE 2

Magnetic resonance imaging of a follicle-stimulating hormone–secreting pituitary macroadenoma with suprasellar extension in a 43-year-old woman.



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ination, were consistent with follicular cystic changes of the ovaries. The patient had a normal postoperative course. Final histologic evaluation of the ovaries revealed benign ovaries containing multiple follicular cysts.

Two weeks after her abdominal surgery, laboratory tests (see [Table 1](#)) revealed an estradiol level of 62 pg/mL, an FSH level of 56 mIU/mL, and an LH level of 1.1 mIU/mL. The inhibin A level was <10 pg/mL. Thyroid stimulating hormone, growth hormone (GH), and cortisol levels were normal (0.75 mIU/mL, 1.0 ng/mL, and 5.2 μ g/dL, respectively). However, her prolactin level was 64.2 ng/mL. An MRI of the pituitary was obtained and revealed a 6.1-cm pituitary macroadenoma with a 3.3-cm extension above the sella turcica resulting in compression of the optic chiasm and nerve on the right ([Fig. 2](#)). On further questioning, the patient reported loss of visual acuity in her right eye over the preceding 2 years, and occasional headaches. The patient was subsequently lost to follow-up, after multiple attempts to reach her failed.

DISCUSSION

The diagnosis of gonadotroph adenomas is elusive. These tumors do not commonly secrete intact gonadotropins in large amounts, and thus cause no specific symptoms other than those associated with a mass effect in the sella turcica

(1). In a review of 100 documented cases of gonadotroph adenomas in men and women, Young et al. (3) found visual disturbance (43%), symptoms of hypopituitarism (22%), and headache (8%) to be the common presenting symptoms, while 17% of cases were diagnosed incidentally. The majority of such tumors in women are found in the postmenopausal years, when the ovaries are incapable of responding to elevated gonadotropin levels produced by the adenoma, thus precluding ovarian hyperstimulation as a common clinical presentation. Moreover, in postmenopausal women, an elevation in gonadotropins is normal, rendering such laboratory tests noncontributory (2). However, when a gonadotroph adenoma is present in the premenopausal woman, the functioning ovary may respond to elevated FSH levels, thus leading to more predictable clinical scenarios.

All three of our patients with gonadotroph adenomas reported new onset menstrual irregularities and/or infertility, which began 2 to 5 years before presentation. Similar complaints have been noted in most other reports (5–10). Transvaginal ultrasonography in our patients revealed large ovaries (7 to 13 cm in greatest diameter) with multiple adjacent cysts ranging in size from 15 to 45 mm, similar to findings in previously reported cases (5–11). All of our patients exhibited a similar hormonal profile with markedly elevated estradiol levels (500–3,944 pg/mL), normal to elevated FSH levels (4.9–18.5 mIU/mL), and markedly suppressed LH

TABLE 2**Hormone levels and tumor sizes previously reported in patients with gonadotroph adenomas.**

Study	Estradiol (pg/mL)	Inhibin A (pg/mL)	FSH (mIU/mL)	LH (mIU/mL)	Prolactin (ng/mL)	Testosterone (ng/dL)	Adenoma size (mm)
Djerassi et al. (4)	>500	—	9.7–18.5	<0.5	50.7	—	18
Välimäki et al. (5)	528–790	173	4.9–8.1	0.3–0.6	—	37.5	12–14
Castelbaum et al. (6)	147–562	—	4.6–7.5	0.2	—	Normal	13
Catargi et al. (7)	405	—	15.3	0.9	261	—	30
Christin-Maitre et al. (8)	7,302	254	4.9	2.4	503	201.7	40
Pentz-Vidovic et al. (9)	1,676	—	13.4	0.5	70	83.6	28
Shimon et al. (10)	29	—	8.4–9.2	0.01	61–71	—	30

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levels (see Table 1), again consistent with prior reports (4–10) (Table 2). Furthermore, all patients had mildly elevated prolactin levels.

When ovarian hyperstimulation with elevated serum estradiol levels occurs in the face of unsuppressed FSH, autonomous production of gonadotropins by the pituitary is the likely explanation. Administration of clomiphene citrate (11) or exogenous gonadotropins (12, 13) can potentially simulate such a clinical scenario, which is plausible in an infertile patient but may be ruled out with a directed history and physical examination (e.g., bruising at injection sites).

Patients with polycystic ovary syndrome (PCOS) also present with menstrual irregularities and infertility, but the menstrual irregularity is rarely a new symptom. In contrast, when a gonadotroph adenoma arises in a reproductive-aged woman, marked and prolonged elevation in estradiol levels and suppressed levels of LH (no LH surge) lead to new onset anovulation, with resulting oligomenorrhea. Moreover, although women with PCOS often present with mildly enlarged polycystic ovaries, cysts rarely exceed 10 mm and are peripherally arrayed about an enlarged hyperechogenic central stroma (14). In contrast, in our patients, ovaries were markedly enlarged and contained cysts which tended to be at least 15 mm in greatest diameter and adjacent to one another with few intervening stroma. Furthermore, elevated LH with normal FSH levels are commonly found in PCOS, while the opposite was evident in our three patients with gonadotroph adenomas and in previously reported patients, in whom LH levels did not exceed 2.4 mIU/mL (see Table 2).

When present in premenopausal women, GCTs may present with menstrual irregularity, menorrhagia, or secondary amenorrhea, and, rarely, infertility as the initial manifestation, making the clinical presentation similar to premenopausal women with a gonadotroph adenoma. However, the majority of such ovarian tumors commonly present during the perimenopausal or early postmenopausal period, with a median age of diagnosis between 50 and 54 years (15). Furthermore, GCTs of the ovary most commonly appear as unilateral, well-defined, unlobulated solid masses with scat-

tered internal cystic portions or septated cystic masses on ultrasonographic imaging (16, 17). Mean size ranges from 10 to 15 cm, and MRI of such tumors may reveal evidence of hemorrhage, a common and characteristic finding of GCT (18). All three of our patients with a gonadotroph adenoma presented with multicystic adnexal masses that lacked any solid component, were bilateral, and showed no evidence of hemorrhage. As with GCT, two of our patients with elevated estradiol levels also had elevated inhibin A levels (213–617 pg/mL). However, in none of the cases were FSH levels suppressed, an unexpected finding when both estradiol and inhibin levels are significantly elevated, again pointing toward autonomous production of FSH from the pituitary gland.

The mild elevation in prolactin seen in all three of our patients is probably a function of a local mass effect of the gonadotroph adenoma on adjacent lactotrophs, or potentially secondary to an interruption of release of dopamine from the hypothalamus (in the case of larger macroadenomas). In the face of elevated levels of FSH, hyperprolactinemia is unlikely to be caused by a prolactin secreting adenoma.

Pituitary imaging is necessary to make the diagnosis of a gonadotroph adenoma. Magnetic resonance imaging revealed pituitary macroadenomas in two of our patients (17 mm and 61 mm, in largest diameter) as well as in all previously reported cases (12–40 mm) (see Table 2). One of our patients (patient 1) was diagnosed with a microadenoma (9 mm), the first such report in a woman with a gonadotroph adenoma and ovarian hyperstimulation. It is likely that, with an increased awareness of the diagnosis, more cases of gonadotroph adenoma will be diagnosed at the microadenoma stage, before further enlargement of the tumor leads to central nervous system symptoms.

In conclusion, a gonadotroph adenoma should be considered in a reproductive-aged woman who presents with a history of new onset menstrual irregularities and/or infertility, bilaterally moderately enlarged multicystic ovaries, and elevated estradiol levels. In addition to a supranormal serum estradiol levels, hormonal evaluation should also reveal a

normal to elevated level of FSH, and a suppressed LH level. Imaging with MRI is needed to establish the diagnosis of a pituitary microadenoma or macroadenoma. With a heightened awareness of the presenting signs and symptoms of this syndrome, the appropriate therapeutic intervention can be determined and unnecessary surgery avoided.

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