

Management of infertility and long-term follow-up in women with follicle-stimulating hormone-secreting adenoma

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Follicle-stimulating hormone (FSH)-secreting adenoma (FSHoma) is a relatively uncommon type of gonadotroph adenoma.^[1] The characteristics of this disease in women in the reproductive age include enlarged ovaries with multiple cysts, normal to elevated serum estradiol levels, elevated FSH levels, reduced luteinizing hormone (LH) levels, causally induced menstrual disorder, infertility, and ovarian hyperstimulation. The tumor is always immunopositive for FSH and sometimes immunopositive for LH and prolactin (PRL).

Patients with FSHoma often present to the infertility and reproductive department of a hospital owing to infertility and irregular menstruation. Ultrasound often shows polycystic ovarian enlargement. In some patients, ovarian cystectomy is performed to exclude ovarian tumor; however, this can decrease the chances of ovarian preservation. On the other hand, transsphenoidal pituitary surgery is an important way to manage patients with FSHoma.^[2]

This clinical observation included five patients with FSHoma who were treated at the Reproductive Center of Peking University Third Hospital between January 2007 and December 2018. The study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee (No. 258-01) and the need for informed consent was waived. These five patients received individualized protocols, including *in vitro* maturation (IVM), extra-long protocol, and natural cycle monitoring [Table 1].

Case 1: A 31-year-old woman had been referred to our department 12 years ago because of infertility and irregular vaginal bleeding for 1 year. Repeated transvaginal ultrasound revealed an ovarian cyst. The patient underwent laparoscopic exploration and left oophorectomy. Pathologic examination revealed benign follicular cyst,

and her serum hormone levels were as follows: PRL, 24.4 ng/mL; FSH, 9.86 mIU/mL; LH, <0.6 mIU/mL; estrogen (E2), <73 pmol/L; testosterone (T), 1.42 nmol/L; and androgen (A), 6.3 nmol/L. Magnetic resonance imaging (MRI) revealed a pituitary tumor measuring 14 mm × 22 mm × 20 mm; on the hindsight, the patient recalled a history of headache without visual changes. Transsphenoidal pituitary surgery was conducted at the neurosurgery department. The tumor was immunopositive for FSH and negative for all the other pituitary hormones, including LH, growth hormone (GH), PRL, thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH). Two months after the operation, her hormone levels were normalized. Ovarian size and function were gradually normalized, and ovulation was restored. After transvaginal ultrasound monitoring for seven cycles, the patient became pregnant and delivered a baby at full term. The follow-up of this patient after 12 years showed no recurrence.

Case 2: A 31-year-old woman presented to our department with irregular vaginal bleeding 8 years ago. She had undergone left salpingo-oophorectomy and right oophorectomy for bilateral ovarian cysts 22 years ago and laparoscopic right oophorectomy 10 years ago. Histopathologic examinations revealed an ovarian follicular cyst. Pelvic ultrasound revealed right polycystic ovarian enlargement, measuring 65 mm in diameter. Laboratory testing revealed PRL level of 0.70 ng/mL, FSH level of 5.53 mIU/mL, LH level of 0.54 mIU/mL, and E2 level of 273 pmol/L. MRI revealed a 4 mm × 5 mm pituitary tumor, which was too small for neurosurgery. Therefore, four injections of triptoreline (3.75 mg every 30 days) were administered. After the injections, the ovarian cysts decreased in size, with the right ovary measuring 28 mm × 14 mm. Controlled ovarian stimulation using human menopausal gonadotropin, in conjunction with intrauterine insemination, did not provide adequate

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Table 1: Clinical presentations and treatment in patients with FSHoma.

Patient	Age (years)	Pituitary tumor size (mm)	Headache	Ovarian surgical history	Transsphenoidal tumor resection	IVF/IVM	GnRHa pre-treatment	Live birth	Menstrual irregularity after surgery
1	31	14 × 22 × 20	Y	Y	Y		N	Y	N
2	31	4 × 5	N	Y	N	IVF	Y	Y	Y
3	31	22 × 23 × 24	Y	N	Y	IVM	N	Frozen embryos	Y
4	30	3.5 × 3.5	N	Y	N	IVF	Y	Y	Y
5	30	22.5 × 30.9 × 23.2	Y	N	Y		N	Under treatment	N

FSHoma: Follicle-stimulating hormone-secreting adenoma; IVF: *In vitro* fertilization; IVM: *In vitro* maturation; GnRHa: Gonadotropin releasing hormone agonist; Y: Yes; N: No.

results. Therefore, another dose of gonadotropin releasing hormone agonist was used for the extra-long *in vitro* fertilization (IVF) protocol. The starting dose of recombinant FSH was 225 IU; six oocytes were retrieved, and two embryos (7G1 and 8G1) were transferred on day 3 after oocyte retrieval; at 14 days after transfer, the serum beta-human chorionic gonadotropin (β -hCG) concentration was 719 mIU/mL. Luteal phase support with progesterone (P) was given until 10 weeks of pregnancy. The patient delivered a baby at full term. For several years after the delivery, the patient persistently suffered from enlarged polycystic ovaries and underwent curettage several times owing to irregular vaginal bleeding.

Case 3: A 31-year-old woman was referred to our department 4 years ago owing to 4 years of infertility. Ten years ago, she was diagnosed with pituitary adenoma because of headache and hypomenorrhea. MRI showed a 22 mm × 23 mm × 24 mm pituitary tumor. Eight years ago, she underwent a successful transsphenoidal pituitary surgery for pituitary adenoma. Immunostaining revealed that 20% to 30% of the tumor cells were positive for FSH β , negative for LH β and ACTH, and weakly positive for GH, PRL, and TSH. Four years after the surgery, she presented to our hospital because of irregular menstruation. Pelvic ultrasound revealed bilateral polycystic ovarian enlargement, probably because of the recurrence of the pituitary adenoma, and her hormone levels were as follows: PRL, 23 mIU/mL; FSH, 6.39 mIU/mL; LH, 0.1 mIU/mL; E2, 1817 pmol/L; T, <0.69 nmol/L; and A, 3.43 nmol/L; P, 4.52 nmol/L; and anti-müllerian hormone (AMH), 1.06 ng/mL. The patient underwent IVM treatment without controlled ovarian stimulation. The final oocyte maturation trigger was the injection of 250 μ g human chorionic gonadotropin (HCG) (Ovidrel, Merck-Serono Ltd., Aubonne, Switzerland). Approximately 36 h after HCG injection, transvaginal ultrasound-guided oocyte aspiration was performed. Five oocytes were retrieved, among which four were mature metaphase II oocytes, and three embryos were formed (7G1, 7G1, and 8G1) according to Veeck morphological grading system. At present, the patient has not received embryo transfer because of personal reasons. Follow-up of the patient showed persistent polycystic ovarian enlargement and irregular vaginal bleeding.

Case 4: A 27-year-old woman presented to our center 2 years ago with irregular vaginal bleeding. Her medical and obstetrical histories were unremarkable, except for

irregular menses. Pelvic ultrasound and MRI revealed bilateral polycystic ovarian enlargement, which could not be excluded as a malignant tumor. In 2012 and 2014, she underwent laparoscopy exploration and bilateral oophorectomy. Pathologic examination showed follicular cysts. After the operation, there was recurrence of bilateral polycystic ovarian enlargement. In 2016, she visited our center because of infertility; her hormone levels were as follows: PRL, 16.6 mIU/mL; FSH, 9 mIU/mL; LH, 0.53 mIU/mL; E2, 9189 pmol/L; and AMH, 0.19 ng/mL. The tumor markers carbohydrate antigen (CA) 125 and CA 19-9 were normal. MRI revealed a pituitary tumor, 3.5 mm in diameter, for which we administered three injections of triptoreline (3.75 mg every 30 days). After the injection, ultrasound showed persistence of the bilateral polycystic ovarian enlargement, with hormone levels of PRL 11 mIU/mL, FSH 9.86 mIU/mL, LH 0.5 mIU/mL, and E2 177 pmol/L. At 30 days after the final injection, purified FSH and LH were administered; when the lead follicle was 20 mm × 21 mm in diameter, FSH and LH were discontinued, and HCG was administered. At 36 h after HCG administration, oocyte retrieval was performed via transvaginal ultrasound-guided follicle aspiration; five oocytes were retrieved and two embryos (6G2 and 8G2), according to Veeck morphological grading system, were transferred on day 3 after oocyte retrieval. Luteal phase support continued until the day when pregnancy was confirmed by the blood β -hCG test. We also gave her estrogen and HCG 5000 IU every other day (QOD) to improve the implantation. After the transfer, the blood β -hCG concentration was 929 mIU/mL at 14 days and 35,776 mIU/mL at 23 days. At 30 days after the transfer, ultrasound showed an intrauterine gestational sac with positive cardiac movement. The patient delivered a baby at full term; during cesarean section, oophorectomy was performed. We followed up the patient for 2 years. She continued to have polycystic ovary and menstrual irregularity after delivery.

Case 5: A 30-year-old woman presented to our center 3 years ago because of 3 years of infertility. Transvaginal ultrasound showed bilateral polycystic enlargement, with the hormone levels of PRL 41.6 ng/mL, FSH 12.6 mIU/mL, LH <0.1 mIU/mL, E2 174 pmol/L, TSH <0.69 nmol/L, and ACTH 5.22 nmol/L. MRI demonstrated a 22.5 mm × 30.9 mm × 23.2 mm pituitary adenoma, for which she underwent transsphenoidal pituitary surgery. The tumor was immunopositive for FSH, TSH, and PRL and negative for all the other pituitary hormones, including LH, GH,

and ACTH, as well as for Ki-67 (10%). However, the adenoma recurred, and the patient underwent another transsphenoidal surgery. She is currently scheduled to receive assisted reproductive treatment at our department.

Hormone-secreting tumors produce specific hormones at high levels. However, in patients with FSHoma, the FSH level is normal or only slightly elevated but can cause ovarian hyperstimulation. In our patients, as well as in many other cases reported in literature, the correct diagnosis of FSHoma was made several years after the onset of the gynecologic symptoms; some patients had even undergone salpingo-oophorectomy or oophorocystectomy despite thorough hormone evaluation. In women of the reproductive age, the characteristics of the disease are enlarged ovaries with multiple cysts, inappropriately elevated serum E2 levels, normal to mildly elevated FSH levels, suppressed LH levels, menstrual irregularity, spontaneous ovarian hyperstimulation, and infertility.^[3,4]

Functioning FSHomas need to be differentiated from polycystic ovary syndrome (PCOS) and ovarian tumors. In PCOS patients, there is usually an increased LH/FSH ratio associated with clinical or biochemical hyperandrogenism, and the ovaries are only mildly enlarged, with cysts exceeding 1 cm. Awareness of ovarian cysts caused by FSHomas should allow clinicians to avoid misdiagnosis and make the right therapeutic decision. In three of our five patients, correct diagnosis was delayed and oophorocystectomy was performed; two of these three patients underwent ovarian surgery twice, and one of them even received left salpingo-oophorectomy. These procedures are detrimental to the ovarian function of infertile patients. Therefore, in patients with polycystic ovaries complicated with infertility and irregular vaginal bleeding, and whose serum hormone measurements show normal to elevated serum estradiol levels, elevated FSH levels, and reduced LH levels, MRI should be performed to exclude pituitary adenoma, which may be FSHomas.

Among the patients in our study, the longest follow-up was 12 years. Notably, in the patients who underwent neurosurgery, complete resection resulted in resolution

of symptoms and normalization of the hormone levels; whereas incomplete resection resolved only the neurologic symptoms but not the FSHoma endocrine symptoms, as exemplified by the case that achieved pregnancy by IVF but had recurrent ovarian enlargement and menstrual irregularity after delivery. Therefore, for such cases, surgical intervention is the first choice.

This study may provide us with some clues on how to help infertile FSHoma patients to become pregnant. To the best of our knowledge, this is the first article that describes the treatment of infertile FSHoma patients.

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Conflicts of interest

None.

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