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*Case Report*

# Successful ovarian stimulation and pregnancy in an infertile woman with Rathke's cleft cyst: a case report

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**Abstract:** Purpose: To report a case of successful ovarian stimulation and pregnancy in an infertile woman with Rathke's cleft cyst (RCC). Methods: This is a case report of a 32-year-old infertile woman with RCC presenting with secondary amenorrhea and hypogonadotropic hypogonadism (HH). Three rounds of ovarian stimulation and ovulation induction by means of HMG and HCG were performed (two before HSG and one after HSG). HSG was performed after two rounds of ovulation induction without pregnancy to assess the fallopian tubes and uterine cavity of the patient. Serum beta-human chorionic gonadotropin (β-HCG) and ultrasound examination were performed after the third round of ovulation induction to confirm successful pregnancy. Results: HSG revealed that the uterine cavity was normal and that the bilateral fallopian tubes were unobstructed. Four weeks after the third round of ovulation induction, the β-HCG test was positive (10261 μg/L), and ultrasound examination showed an intrauterine early gestational sac with an embryo (10*7 mm) and a primitive heart tube pulse. Conclusions: Infertility accompanied by RCC is rare in the clinic. Clarifying the cause of infertility and secondary amenorrhea is very important for achieving a successful pregnancy. This case demonstrates that such infertility can be treated effectively with ovarian stimulation and ovulation induction using HMG and HCG. To the best of our knowledge, this is the first case report of infertility accompanied by RCC.

**Keywords:** Secondary infertility, Rathke's cleft cyst (RCC), secondary amenorrhea, ovarian stimulation, ovulation induction

## Introduction

Rathke's cleft cysts (RCCs) are intrasellar and/or suprasellar lesions that originate from em bryonic remnants from the incomplete obliteration of Rathke's pouch [1]. They are the most commonly discovered sellar abnormality and are found in 13-33% of routine autopsies [2].

Most RCCs are asymptomatic. However, when they are large enough, they will result in symptoms, commonly including headache, visual disturbance and varying degrees of pituitary dysfunction. Between 19% and 81% of RCC patients present with anterior pituitary hormone deficits, including hypogonadism with amenorrhea and/or galactorrhea (amenorrhea-galactorrhea syndrome) [3, 4]. To our knowledge, female infertility associated with RCCs has rarely been reported to date.

Here, we report a case of successful ovarian stimulation and pregnancy in an infertile woman with RCC presenting with secondary amenorrhea and hypogonadotropic hypogonadism (HH). The literature relating to this rare clinical condition was briefly reviewed.

## Case report

A 32-year-old woman was admitted to our reproductive center seeking subfertility services for secondary infertility and amenorrhea. She experienced menarche when she was 14 years old and had a regular menstrual cycle with an interval of 28-30 days. She conceived spontaneously in 2007 and delivered a healthy male baby in 2008. After her first spontaneous delivery, she gradually became amenorrheic. In 2010, she sought gynecological care for secondary amenorrhea in another hospital and

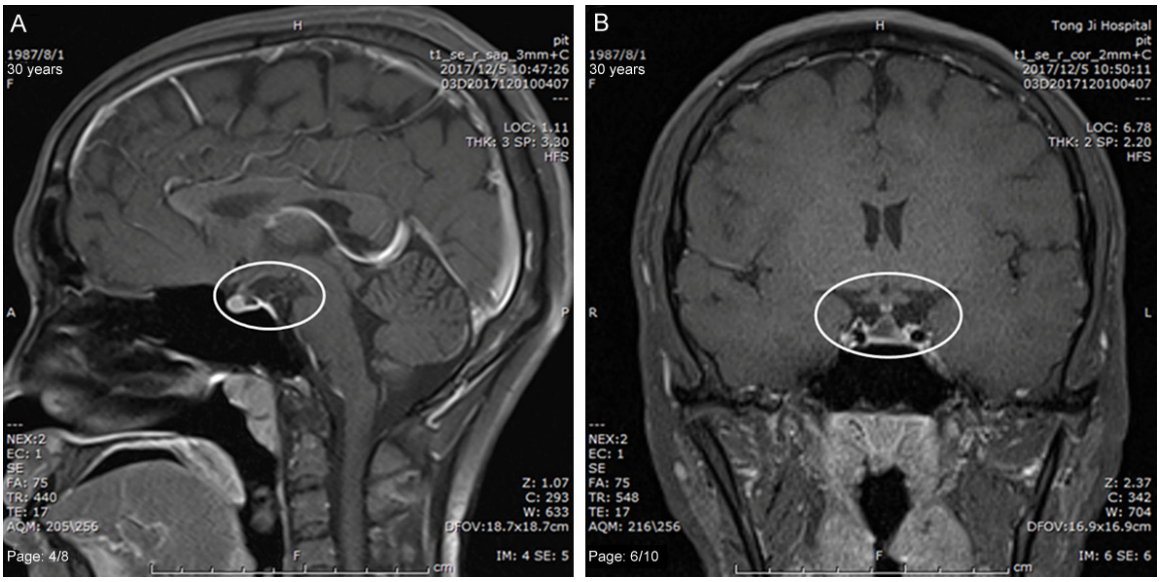


**Figure 1.** MRI sagittal (A) and coronal (B) sections of the brain demonstrating a 5.4*3.0 mm Rathke's cleft cyst in the pituitary.

was treated with an artificial hormone cycle (estrogen and progestogen), which failed to induce menarche.

However, in 2012, she conceived spontaneously and underwent cesarean section at 37 weeks because of placental abruption and hemorrhage. Unfortunately, the baby did not survive. After this pregnancy, she used condoms to prevent pregnancy for two years. With the intention of another baby, she stopped contraception but failed to conceive.

After her second pregnancy in 2012, she continued to have amenorrhea until June 2020. To identify the cause of amenorrhea, in 2017, a brain MRI was conducted and revealed a 5.4*3.0 mm RCC in her pituitary (**Figure 1**). The cyst was not treated by a neurosurgeon since this patient did not present with headaches or visual disturbances but only with amenorrhea. In June 2020, she went to our reproductive center for consultation regarding infertility and amenorrhea.

The baseline characteristics of the patient are shown in **Table 1**. Although her AMH levels were normal, FSH, LH, estradiol and prolactin levels were below the normal range. Furthermore, progesterone levels were at follicular-stage levels. Her thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels were normal. Laboratory examinations revealed that her ovarian reserve and thyroid function were normal but that her hypothalamic function was insufficient.

At the same time, we assessed the antral follicle count (AFC) by ultrasonography. It revealed that the left AFC was 3, that the right AFC was 5, and that there was no dominant follicle; additionally, her endometrial thickness was 1 mm, and her uterus was small (24*17*22 mm). To confirm this result, she underwent three-dimensional (3D) ultrasound examination of uterus and adnexa: the uterine morphology was normal, uterine size was 2.5*2.0*2.6 cm, endometrial thickness was 0.15 cm, left ovary size was 2.0*1.1 cm, and right ovary size was 2.0*1.4 cm. These two ultrasonography results were consistent and revealed that not only the uterus but also the bilateral ovaries were atrophied.

Combining the laboratory examinations and ultrasonography results, the most possible etiology of atrophy of the ovaries and uterus, amenorrhea and infertility is chronic deficiencies in estrogen and gonadotropins. To clarify the diagnosis and response of oocytes to FSH/LH stimulation, we had the patient undergo ovulation induction treatment by using human menopausal gonadotropin (HMG, Lizhu Pharmaceutical Factory, China). When the dominant

**Table 1.** Clinical characteristics of the patient

| Characteristic | Value | Normal value range |
|---|---|---|
| Age | 32 | |
| BMI (kg/m$^2$) | 22.03 | |
| Hormone levels | | |
| FSH (mIU/ml) | 4.41 | Follicular phase: 2.5-10.2; Ovulatory period: 3.4-33; Luteal phase: 1.5-9.1; Menopause: 23-116.3 |
| LH (mIU/ml) | 1.38 | Follicular phase: 1.9-12.5; Ovulatory period: 8.7-76; Luteal phase: 0.5-16.9; Menopause: <0.1-1 |
| $E_2$ (pg/ml) | 18.93 | Follicular phase: 19.5-144.2; Ovulatory period: 63.9-356.7; Luteal phase: 55.8-214.2; Menopause: 0-32.2 |
| P (ng/ml) | 0.21 | Follicular phase: 0-0.91; Menopause: 0-0.39; Luteal phase: 2.65-21.1 |
| T (ng/dl) | 22.96 | Before menopause: 9.01-47.94; Menopause: <7.00-45.62 |
| PRL (ng/ml) | 2.16 | Non-pregnancy: 2.8-29.2; Pregnancy: 9.7-208.5 |
| HCG (mIU/ml) | <2.00 | Non-pregnancy: 0-10; Pregnancy: >10 |
| TSH (μIU/ml) | 1.51 | 0.27-4.20 |
| fT3 (pmol/l) | 5.80 | 3.1-6.8 |
| fT4 (pmol/l) | 17.3 | 12-22 |

Note: BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; $E_2$ = estradiol; P = progesterone; T = testosterone; PRL = prolactin; HCG = human chorionic gonadotropin; TSH = thyroid-stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine.

follicle diameter reached 21.1 mm, 6000 IU human chronic gonadotropin (HCG, Lizhu Pharmaceutical Factory, China) was injected intramuscularly to induce ovulation. At the same time, the patient was asked to have coitus every other day. Three days later, ultrasound examination confirmed ovulation. The patient was treated with dydrogesterone (Abott Biologicals B.V. the Netherlands) 10 mg twice daily for luteal support. Ten days later, she menstruated, indicating failure to conceive in this cycle.

On the second day of her menstruation, the ultrasonogram revealed that there were 4 antral follicles (3-4 mm) in the left ovary and 3 antral follicles (3-4 mm) in the right ovary, and the endometrial thickness was 6.0 mm. We started the second ovulation induction by using HMG. At the same time, we monitored follicle development. When the dominant follicle diameter reached 20.3 mm, 6000 IU HCG was injected intramuscularly to induce ovulation. The patient was asked to have coitus every other day. Three days later, ovulation was confirmed by ultrasound examination. As before, the patient was treated with dydrogesterone 10 mg twice daily for luteal support. Unfortunately, she failed conceived again.

After two cycles of ovulation induction without pregnancy, it was necessary to ensure that her fallopian tubes were unobstructed. Therefore, hysterosalpingography (HSG) was performed after her menstrual period. The uterine cavity was normal, and bilateral fallopian tubes were unobstructed (**Figure 2**). Therefore, one month later, we started the third cycle of ovulation induction using the same protocol as before. The patient had ovulation followed by coitus and luteal support. Four weeks later, the patient showed positivity for serum beta-human chorionic gonadotropin (β-HCG, 10261 μg/L), and ultrasound examination showed an intrauterine early gestational sac with an embryo (10*7 mm) and a primitive heart tube pulse. She became pregnant successfully. On January 4$^{th}$, 2021, her ultrasound examination showed an intrauterine gestational sac (5.6*4.1 cm) with a fetus inside, a crown-rump length (CRL) of 4.1 cm, and a fetal heart pulse.

## Discussion

In this case, the patient's main complaint was infertility for six years, which was a very common complaint in the reproductive center. However, her medical history and situation were complex. The patient's menstruation was regular before her first pregnancy; however, she presented with amenorrhea after her first spontaneous delivery when she was 20 years old. In addition to secondary amenorrhea, there were several key factors: (1) placental abruption and hemorrhage in her second pregnancy; (2) failure of artificial hormone cycle (estrogen and progestogen) treatment to induce menstruation; and (3) RCC revealed by MRI. Therefore, the differential diagnosis in such cases should include RCC, premature ovarian failure, Sheehan's syndrome, and intrauterine adhesion, and the diagnosis should be made with caution.

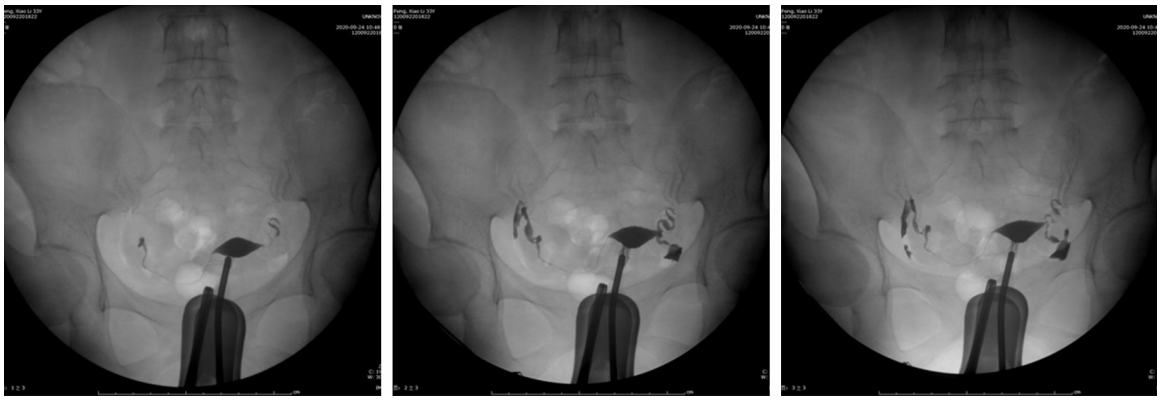

**Figure 2.** HSG imaging demonstrating a normal uterine cavity and unobstructed bilateral fallopian tubes.

First, although this patient had a history of placental abruption, intrapartum hemorrhage and cesarean section during her second spontaneous pregnancy, her menstruation had ceased after her first spontaneous labor. Furthermore, MRI images without partial empty sella in the pituitary also did not support the diagnosis of Sheehan's syndrome [5, 6].

Second, premature ovarian failure was excluded because her AMH levels and AFC were in the normal range. 3D ultrasound examination revealed small ovaries, a small uterine size and a thin endometrium that were consistent with her low estrogen level. This means that the patient was chronically deficient in estrogen without the development of follicles.

Intrauterine adhesion was another diagnosis that should be considered because of the failure of the artificial hormone cycle (estrogen and progestogen) treatment in 2010 and her history of cesarean section. However, 3D ultrasound examination and HSG (**Figure 2**) revealed that the uterine cavity was normal. In the following three cycles of ovulation induction, menstruation was induced successfully. Therefore, intrauterine adhesion could be excluded.

In this case, the patient's menstruation was regular before her first pregnancy; however, she presented with amenorrhea after her first spontaneous delivery when she was 20 years old. A RCC (5.4*3.0 mm) was detected by MRI because of her amenorrhea in 2017. Owing to slow growth, RCCs are commonly silent before middle age. The peak onset age ranges from 30-50 years, with an average age of 34-44 years. The clinical manifestations are obvious when the cysts are swollen enough to compress the surrounding tissues [4]. Headaches (33-81% of patients), visual disturbance (12-58% of patients), and pituitary hormone abnormalities (19-81% of patients) are the most prevalent symptoms [4]. Among the patients with pituitary hormone abnormalities, 39% show panhypopituitarism, 25% amenorrhea-galactorrhea syndrome, 13% diabetes insipidus, and 6.8% elevated prolactin levels alone [7]. Because the size of the cyst in this case was small, there were no compressive syndromes (such as headache or visual disturbance).

Originating from Rathke's cleft in the vestigial pars intermedia of the pituitary gland, RCCs are benign cysts that are predominantly intrasellar lesions. The contents inside the cysts are usually thick, mucoid, or gelatinous and are wrapped in a delicate membrane [8]. It has been proposed that the contents of RCCs cause an inflammatory reaction in the cyst wall and adjacent tissue, resulting in the adjacent pituitary destruction and the pituitary function loss [9, 10]. The low levels of FSH, LH, $E_2$, P and PRL in this case may be caused by this kind of inflammatory reaction. Chronic deficiencies in estrogen and gonadotropins may be the etiology of atrophy of the ovaries and uterus, amenorrhea and infertility. To best of our knowledge, this is the first case report of infertility caused by RCC.

For symptomatic RCCs, a surgical approach is the first-line treatment, while recovery of pituitary function after surgery differs considerably according to the damage to the pituitary [4]. P. Trincado et al. reported an 18-year-old male who presented with symptomatic RCC with hypogonadotropic hypogonadism, with all other

endocrine results within the normal ranges [11]. Although no evident recurrence occurred by the time of the report, the patient developed panhypopituitarism due to surgery. A Chinese team also reported a case of RCC with hypogonadotropic hypogonadism in a middle-aged man. After the cyst was removed by surgery, testosterone replacement therapy was given [12], the effect of which was unknown owing to the lack of follow-up. Considering that, except for pituitary dysfunction, there were no other symptoms (such as headache or visual disturbance) in this case, surgery was not suggested.

In this case, infertility was the chief complaint of this RCC patient, and except for pituitary dysfunction, there were no other symptoms (such as headache or visual disturbance). Therefore, ovulation induction treatment was given instead of surgery. Gonadotropin therapy for pituitary dysfunction is known to be effective in promoting sexual development and in inducing ovulation and pregnancy [13, 14]. HMG was given to stimulate follicular development directly. Subsequently, HCG was administered to LH surge and ovulation induction. It is challenging to treat patients with pituitary dysfunction. The ovarian response cannot be predicted precisely and may differ substantially from that of normal patients. To avoid multiple pregnancy and ovarian hyperstimulation syndrome (OHSS), the patient should be treated with a longer duration of stimulation with gradual stepping up of the dose to reach the threshold of FSH and LH. In the first two cycles of ovulation induction, ovulation was induced successfully, but pregnancy was not achieved.

After the first two cycles of ovulation induction without pregnancy, hysteron-salpingography (HSG) was performed using ethiodized poppyseed oil (Hengrui, China) as contrast. The size, shape and position of the uterine cavity were normal, and bilateral fallopian tubes were unobstructed. After two rounds of ovulation induction, the size of the uterine cavity had recovered to normal. Subsequently, the third round of ovulation induction treatment was given. After ovulation, the patient achieved pregnancy successfully. In 2015, the American Society for Reproductive Medicine (ASRM) indicated that "hysterosalpingography (HSG), using either a water- or lipid-soluble contrast media, is the traditional and standard method for evaluating tubal patency and may offer some therapeutic benefit" [15]. Oviduct flushing directly increases pregnancy rates in the months after HSG [16]. In 2017, Kim Dreyer, et al. [17] reported a multicenter, randomized trial comparing the therapeutic benefit of oil-based and water-based contrast in HSG within 6 months after randomization. They demonstrated that rates of ongoing pregnancy and live births were higher in women receiving HSG with oil contrast than in women receiving this procedure with water contrast. In this case, in the first month after HSG, the patient successfully got pregnant.

## Conclusions

Infertility associated with RCC is rare in the clinic. The medical history of the patient was complex, and the diagnosis was difficult to make because of the large list of potential diagnoses. Chronic deficiencies in estrogen and gonadotropins caused by RCC are the etiology of atrophy of the ovaries and uterus, amenorrhea and infertility. This kind of infertility can be effectively treated with ovarian stimulation and ovulation induction. We hope to share our experience of this case and help other clinicians treat patients in similar situations effectively.

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## Disclosure of conflict of interest

None.

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