Recovery of HPA Axis Function After Successful Gonadotropin-Induced Pregnancy and Delivery in a Woman With Panhypopituitarism

Case Report and Review

Yi Wang, MD, Qiongyue Zhang, MD, Jianzhi Yang, MD, Xiaolong Zhao, MD, Min He, MD, Xuefei Shou, MD, Shiqi Li, MD, Yiming Li, MD, Yongfei Wang, MD, and Hongying Ye, MD

Abstract: Hypopituitarism is defined as the partial or complete defect of anterior pituitary hormone secretion. Patients with hypopituitarism usually need life-long hormone replacement therapy. However, in this case, we report a patient with panhypopituitarism whose hypothalamus–pituitary–adrenal (HPA) axis function was completely recovered after pregnancy and delivery.

In this case study, we report the case management and conducted a review of literature to identify the possible mechanism of pituitary function recovery.

The patient who suffered from secondary amenorrhea was found a nonfunctioning pituitary macroadenoma, and the hormone test showed serum cortisol, FT3, FT4, TSH, and PRL were at normal range. After surgical removal of the tumor which invasion in the sellar region, the patient had panhypopituitarism confirmed by the routine hormone test. Though spontaneous pregnancy is impossible in female patients with panhypopituitarism, the patient was restored fertility by the help of artificial reproductive techniques. After the confirmation of the pregnancy, levothyroxine was increased to 75 µg daily and readjusted to 150 µg daily before delivery according to the monthly measurement thyroid function. Hydrocortisone 10 mg daily replaced cortisone acetate; the dose was increased according to the symptoms of morning sickness. A single stress dose of hydrocortisone (200 mg) was used before elective cesarean delivery and was tapered to the dose of 10 mg per day in 1 week. Levothyroxine was reduced to 75 µg daily after delivery. During follow-up, her hypothalamus–pituitary–adrenal (HPA) axis function was completely recovered. The peak serum cortisol level could increase to 19.08 µg/dl by insulin-induced hypoglycemia. However, growth hormone remained unresponsive to the insulin-tolerance test, and thyroid hormone still needed exogenous supplementation.

Hormone replacement therapy needed closely followed by endocrinologist and multidisciplinary cooperation during the pregnancy of patients with hypopituitarism. This case indicates that the pituitary function may partially recover after pregnancy in panhypopituitarism patients.

INTRODUCTION

The anterior pituitary orchestrates the complex regulatory functions of multiple target endocrine glands. Hypopituitarism is defined as the partial or complete defect of anterior pituitary hormone secretion, which may result from pituitary macroadenoma or other sella region tumors, also not rare after pituitary surgery. Other causes such as irradiation, brain trauma, infarction, subarachnoid hemorrhage may also cause hypopituitarism. Most patients with hypopituitarism need lifelong hormone replacement therapy. A small amount of patients resulting from compressive pituitary macroadenoma may be reversed by surgical decompression, and rare cases of spontaneous recovery from hypopituitarism due to postpartum hemorrhage or brain trauma.

Gonadotropin deficiency in women with hypopituitarism causes infertility. Although advances in artificial reproductive techniques (ARTs) provide methods to restore fertility in hypopituitary women, only few cases of successful pregnancy and parturition have been published, reporting high rates of obstetric complications. Optimizing the strategy of hormone replacement based on the physiological changes of pituitary hormone axes during pregnancy in healthy women is necessary for the successful pregnancy and delivery. And the placenta is now looked as a new source of hormone during pregnancy. However, the potential effects of pregnancy on the pituitary function of hypopituitarism patients are not clear. Here we report a case of panhypopituitarism patient resulting from pituitary macroadenoma, whose HPA axis function was completely recovered after successful gonadotropin-induced pregnancy and delivery.

Case Report

This study was approved by Hushan Hospital ethic committee and with informed consent from the patient. With MRI scanning (Figure 1) and routine hormone test (Table 1), nonfunctioning pituitary macroadenoma was found on a woman...
who suffered from secondary amenorrhea at the age of 30. The hormone test showed serum cortisol, FT3, FT4, TSH, and PRL were at normal range, which suggested that both HPA and HPT axes were intact. Pituitary MRI scanning showed macroadenoma invasion in the sellar area. Craniotomy operation via the interhemispheric approach was successfully performed. And nonfunctioning pituitary adenoma was confirmed by the immunohistological staining. After operation, the hormone retest showed the blunted anterior pituitary function, without symptoms of diabetes insipidus. Cortisone acetate (25 mg daily), levothyroxine (50 µg daily), and complex packing estradiol valerate tablet were taken as replacement therapy for the panhypopituitarism after operation.

The patient was enrolled for the evaluation and optimization of hormone replacement therapy and consultation for the pregnancy 7 months after the operation. Blood was sampled before cortisone acetate and levothyroxine were taken at 8:00 AM in the morning. The results of hormone measurement showed that FT3 and FT4 were at the target level, serum cortisol in the morning was 7.8 µg/dL but serum cortisol 2-h after the cortisone acetate taken was higher than the upper level of normal range in the morning. So the insulin tolerance test was performed to evaluate the integrity of the HPA axis. Thirty minutes after insulin bonus injection, plasma glucose decreased to 1.7 mmol/L, and serum cortisone only elevated to 11.05 µg/dL (Figure 2, Table 2). These results suggested the insufficiency of HPA axis; the dose of cortisone acetate was reduced from 25 to 12.5 mg daily. The peak value of growth hormone (GH) in the insulin tolerance test was 0.1 mU/L (Table 2). The LHRH stimulation test was also undertaken and showed no response of LH and FSH upon 100 µg LHRH stimulation (data not shown). MRI scanning (Figure 3A) showed no evidence of residual tumor or recurrence.

After optimizing the replacement therapy, ovulation was induced by the injection of human menopausal gonadotrophin (HMG) following human chorionic gonadotrophin (HCG) at a large dose, which was conducted by a physician specialized in reproductive medicine. The patient was becoming pregnant with the first cycle. After the confirmation of the pregnancy, levothyroxine was increased to 75 µg daily and readjusted to 150 µg daily before delivery according to the monthly measurement of FT3 and FT4. Hydrocortisone 10 mg daily replaced cortisone acetate; the dose was increased to 10 mg in the morning, 5 mg at noon, and 5 mg at dinner due to the symptom such as nausea, vomiting, and fatigue at 8 weeks gestational age (GA). Elective cesarean delivery on request was performed.

### TABLE 1. Hormone Levels Before Surgery, After Surgery, Before Pregnancy and After Delivery

|                | FT3  | FT4  | TSH  | GH   | F    | PRL  | FSH  | LH   | E2   | P    |
|----------------|------|------|------|------|------|------|------|------|------|------|
| Before surgery | 3.84 | 15.7 | 1.52 | 0.8  | 17.68| 16.54| 10.07| 2.12 | 130.6| 2.6  |
| After surgery  | 2.2  | 14.97| <0.11| 1.4  | 3.17 | 3.46 | 2.42 | 0.26 | 73.3 | NA   |
| Before pregnant| 3.54 | 15.73| <0.02| <0.1 | 8.75 | 25.8 | <0.2 | <0.14| 429.4| 0.2  |
| After delivery | 4.05 | 21.6 | 0.001| 0.061| 11.72| 23.88| 0.37 | 0.1  | 168.6| 0.4  |

E2 = estrogen; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; P = progestin; PRL = prolactin; TSH = thyrotropic hormone.

*25 mg cortisone acetate taken 24 h before sampling.

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without complications under combined spinal–epidural anesthesia at 39 \(\pm\) 1 weeks’ GA and a viable fetus was delivered (female, 3750 g, height 50 cm, Apgar score 10). For surgery, the patient received a single stress dose of hydrocortisone (200 mg) that was tapered to the dose of 10 mg per day in 1 week. After delivery, levothyroxine was reduced to 75 mg daily and serum FT3 and FT4 were kept at the ideal level. The baby was breast-fed accompanied with artificial fed.

Half year after postpartum, the patient was enrolled again for the evaluation because she did not feel any discomfort when missing hydrocortisone. So, the insulin tolerance test was repeated to evaluate the integrity of the HPA axis after the withdrawal of hydrocortisone for 2 weeks. The peak serum cortisol level increased to 19.08 \(\mu\)g/dL by insulin-induced hypoglycemia (Figure 2, Table 3). The normal responsive curve of serum cortisol suggested a complete recovery of HPA axis. So, the patient continued the levothyroxine at the dose of 75 \(\mu\)g daily and restarted the complex packing estradiol valerate tablet. Growth hormone still do not response to insulin-induced hypoglycemia; the peak value was 0.1 mU/L (Table 3). However, pituitary MRI scanning showed local recurrence and further enlargement of the residual tumor (Figure 3B). The patient had accepted trans-sphenoidal surgery to remove the tumor totally. Histoimmuostaining showed strong positive staining of ACTH.

**DISCUSSION**

Spontaneous pregnancy in patients with pituitary dysfunction were only reported in partial hypopituitarism patients with normal gonadal function, most commonly in Sheehan’s syndrome or lymphocytic hypophysitis.9,10 Panhypopituitarism patients could not be spontaneous pregnant, clinical practice of ovulation–induction treatment including administration of hCG and FSH, pulsatile GnRH, and *in vitro* fertilization, enabled the hypopituitary women to become ovulation and pregnancy. However, limited experience showed that the success rate was less lower than other no ovulation infertility. The Reproductive Medicine Unit and the Department of Endocrinology in University College London Hospitals provided ovulation–induction treatment for 19 pituitary dysfunction women in the past 20 years. Those 19 patients underwent fertility

**TABLE 2.** Serum Levels of Glucose, Cortisol, ACTH, and Growth Hormone During Insulin-Induced Hypoglycemia (Before Pregnancy)

| Min  | 0    | 30   | 45   | 60   | 90   | 120   |
|------|------|------|------|------|------|-------|
| Glucose (mmol/L) | 4.1  | 1.7  | 2.4  | 6.3  | 8.8  | 9.6   |
| Cortisol (\(\mu\)g/dL) | 8.75 | 11.05| 10.96| 9.48 | 7.10 | 5.71  |
| ACTH(pg/mL) | 25.2 | 19.8 | 29.6 | 24.8 | 21.1 | 20.9  |
| GH(mU/L) | <0.1 | 0.1  | <0.1 | 0.1  | <0.1 | <0.1  |

GH = growth hormone.
treatment over a total of 164 cycles; almost all women (95%) achieved ovulation. However, ovulation only occurred in 60% of all treatment circles. Nine out of 19 patients (47%) achieved at least 1 pregnancy. Only 8 patients (42%) achieved a live birth. Seven out of 18 pregnancies (39%) miscarried. These data showed relatively low pregnancy rates and a high miscarriage rate in ovulation induction in hypopituitism patients compared with other causes of anovulation. Pituitary hormone deficiency played an important role in the adverse effect on achieving pregnancy.6 Despite the lower rate of pregnancy, the hypopituitary patients were at other increased risks including postpartum hemorrhage occurred in 8.7%, transverse lie in 16%; 42.4% of the newborns were small for gestational age.7

Therefore, hormone replacement therapy in hypopituitary women was crucial during pregnancy. Recent reports suggested increased risks of pregnancy in hypopituitism were caused by uterine dysfunction, which were resulted from maternal cortisol, thyroid hormone, and GH deficiency.7–9 Due to major hormonal changes during pregnancy, the hormone replacement therapy needed closely followed by the endocrinologist and multidisciplinary cooperation. As hepatic corticosteroid-binding globulin production, there were different explanations for the increased free cortisol levels in pregnancy. For example, the placenta secreted CRH during gestation; the mechanism was still unidentified. The previous study demonstrated that the placenta CRH could stimulate the maternal pituitary has not been exactly proven.16 our patient’s HPA axis restored after delivery, perhaps because of the stimulatory effect of placenta CRH on remnant ACTH neurons. However, the local recurrence of tumor in our case after delivery could not be ignored. Although previous studies showed pituitary prolactinoma expansion during pregnancy, especially in macroprolactinomas, pregnancy rarely enlarges the size of nonfunctioning adenomas.17 According to the pathological result of the second surgery, this patient could not be ruled out silent corticotroph adenoma. Silent corticotroph adenomas are pituitary tumors positive on immunohistochemical staining for ACTH but without clinical evidence of Cushing’s disease in the patient.18 They comprise 20% of all corticotroph adenomas and 3 to 19% of nonfunctioning adenomas. Compared with nonfunctional pituitary adenomas, silent corticotroph adenomas may have more cavernous sinus invasion.19 The previous reported recurrence rate between silent corticotroph adenomas and nonfunctioning adenomas was not conclusive. Some studies showed that the overall recurrence rate was similar between these 2 types of pituitary tumors.20,21 However, some studies indicated that patients with silent corticotroph adenomas tend to have more frequent and earlier recurrences than those with nonfunctioning adenomas,19 especially in patients treated with adjuvant radiotherapy. Only few cases with silent corticotroph adenomas will transform to hypercortisolaemia at a later stage in the diseases.18 Whether the local recurrence of tumor in our case was due to the unique pathological type of tumor should be followed in the future studies.

In summary, the hormone replacement therapy needed closely followed by endocrinologist and multidisciplinary cooperation during the pregnancy of patients with hypopituitism. This case indicated that the pituitary function may partially recover after pregnancy in panhypopituitarism, which highlights the potential effects of pregnancy on the pituitary function of hypopituitarism.

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TABLE 3. Serum Levels of Glucose, Cortisol, and Growth Hormone During Insulin-Induced Hypoglycemia (Half Year Postpartum)

|                | Min 0 | 30  | 45  | 60  | 90  | 120 |
|----------------|-------|-----|-----|-----|-----|-----|
| Glucose (mmol/L) | 4.6   | 1.6 | 2.9 | 3.8 | 4.8 | 5.5 |
| Cortisol (µg/dL)  | 11.72 | 16.63 | 19.08 | 17.05 | 14.22 | 9.85 |
| GH (mU/L)        | <0.1  | 0.1 | <0.1 | 0.1 | <0.1 | <0.1 |

GH = growth hormone.
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