

## Abnormal Enlargement of Pituitary Gland during Pregnancy Remitted Spontaneously after Delivery

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Ovulation induction is seldom reported to cause pituitary abnormality and the physiological enlargement of the pituitary gland during pregnancy is asymptomatic. We report a woman who became pregnant after ovulation induction. She had symptomatic pituitary enlargement with a pituitary height of 2 cm on cranial magnetic resonance imaging (MRI) in the second trimester. Her symptoms (headache and blurred vision) improved greatly after delivery but she had absence of lactation. The height of the pituitary gland decreased to 1 cm on the second cranial MRI 40 days after delivery and her third cranial MRI only revealed a mild central bulge in the pituitary gland eight months after delivery. This article shows that the abnormal enlargement of the pituitary gland during pregnancy might remit spontaneously after delivery and these patients might have higher risk of postpartum hypopituitarism. Neurological symptoms and signs should be closely monitored during pregnancy and neurosurgery may not be necessary. Endocrine surveys should be performed regularly after delivery to detect hypopituitarism as early as possible. (*Chang Gung Med J* 2007;30:81-6)

**Key words:** pituitary gland, pregnancy, lymphocytic hypophysitis, ovulation induction.

Recent advances of ovulation induction help many infertile women to become pregnant but they are seldom reported to cause pituitary abnormality. Physiological enlargement of the pituitary gland during pregnancy does not expand to the extrasellar area to cause symptoms.<sup>(1-4)</sup> We present a woman who became pregnant after ovulation induction. An abnormal enlargement of the pituitary gland, which compressed the optic chiasma, was found in the second trimester and regressed gradually after delivery. Only one patient has been reported to have visual disturbance in pregnancy after induction of ovulation but the mechanism was not confirmed.<sup>(5)</sup> We discuss the possibility of spontaneously remitted pituitary enlargement.

### CASE REPORT

This 41-year-old woman had regular menstrual cycles (MC) but she was infertile using no contraceptives for 2 years. After a series of studies, it was confirmed that neither she nor her husband had any anatomic infertility problems. She had a 6-month history of irregular MC in early 2002 and then she received clomiphene to induce ovulation from June 2002 to December 2002. However, she still did not conceive. She received another course of clomiphene (50 mg per day for 5 days) to induce ovulation and then estradiol (5 mg per day for 6 days) to maintain the uterine endometrium in March 2003. Her serum follicular stimulating hormone (FSH) was 7.04 IU/L

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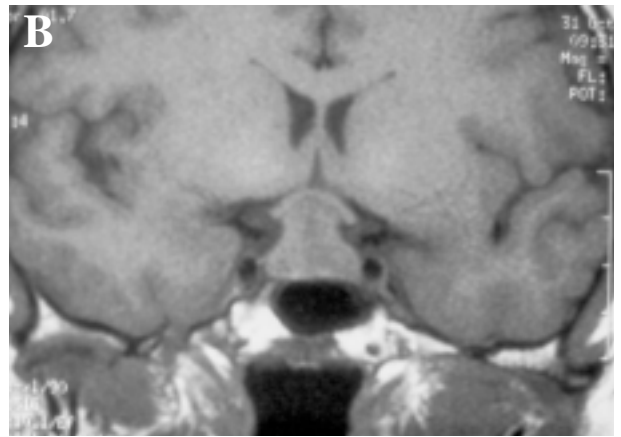
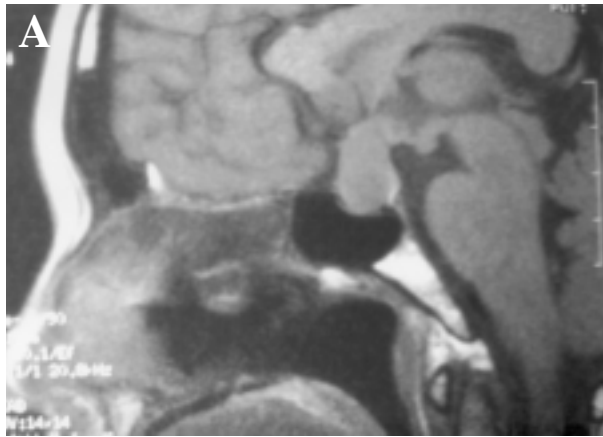
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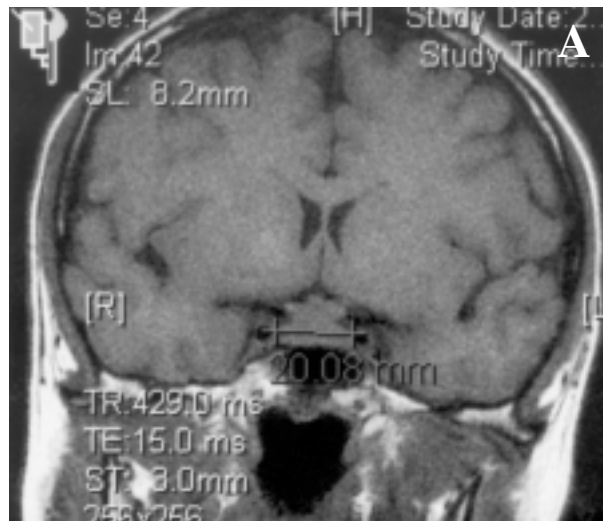
(normal range: follicular phase 3.4-10, mid-cycle 5.7-20, luteal phase 1.9-10), luteinizing hormone (LH) was 1.95 IU/L (follicular phase 1.6-8.3, mid-cycle < 8, luteal phase < 8.1), and 17  $\beta$ -estradiol (E2) was less than 73 pmol/L (follicular phase < 976, mid-cycle 433-1303, luteal phase 462-605) on April 3, 2003. She became pregnant in April 2003. The course of the pregnancy was smooth during the first and early second trimester but left eye pain with blurred vision and subsequent headache developed in September 2003. She visited a neurosurgeon because of headaches, and bitemporal hemianopsia was found. Neither diplopia nor impaired light reflex was noted. Cranial magnetic resonance imaging (MRI)

revealed a large pituitary gland (height: 2 cm), which compressed the optic chiasma (Fig. 1). At that time, the serum prolactin level was 39.69  $\mu$ g/L, which was within normal limits for a pregnant woman. Pituitary apoplexy was suspected initially. As the neurological symptoms did not progress, only observation was advised. She gave birth by cesarean section on January 16, 2004. After delivery, the blurred vision and headache greatly improved but she had absence of lactation. On February 26, 2004, a second cranial MRI revealed that the abnormal pituitary enlargement had decreased to 1 cm in height and only touched the optic chiasma (Fig. 2).

The patient received pituitary function surveys

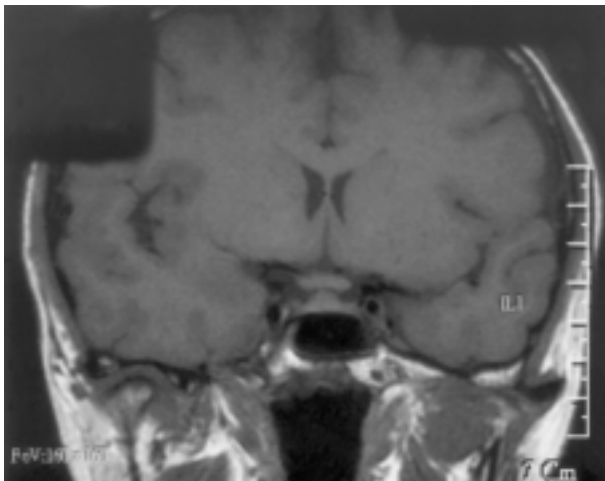


**Fig. 1** The first T1-weighted magnetic resonance imaging on October 31, 2003 (in the second trimester) revealed a large pituitary mass with a height of 2 cm and obvious compression of the optic chiasma. (A: sagittal view; B: coronal view)



**Fig. 2** The second T1-weighted magnetic resonance imaging was performed on February 26, 2004 (forty days after delivery). (A) The coronal view revealed a pituitary mass with a height of 1 cm and mild compression of the optic chiasma. (B) A pituitary mass with homogenous enhancement was seen after intravenous Gd- DTPA. (sagittal view)

in September 2004 because of persistent amenorrhea after delivery. Neither cranial nerve dysfunction nor focal peripheral neurological signs were found. She did not have Cushing's appearance, and still had obvious axillary and pubic hair. On September 15, 2004, a third cranial MRI revealed upper bulging of the central pituitary gland by about 3 mm. (Fig. 3) The serum adrenocorticotropic hormone (ACTH) levels, cortisol, thyroid stimulating hormone (TSH), free thyroxin, growth hormone, E2, FSH and LH were evaluated by chemiluminescent immunoassay. Anterior pituitary dysfunction was noted, including low serum free thyroxin (0.45 ng/dL, normal range: 0.6 ~ 1.75) with inappropriate TSH (4.83  $\mu$ IU/ml), low prolactin (< 1 ng/ml), low morning and afternoon cortisol (both < 1  $\mu$ g/dL) and relatively low ACTH (morning ACTH: 16.6 pg/mL, afternoon ACTH: 9.02 pg/mL). The serum growth hormone level was 0.27 ng/ml (normal range: 0.06~5.0 ng/ml). The serum TSH response to 400  $\mu$ g protirelin (thyrotropin-releasing hormone, TRH test) intravenous injection at 0, 15, 30, 60 and 90 minute was 4.83, 14.0, 18.1, 18.3 and 4.86  $\mu$ IU/ml, respectively. Low serum FSH (1.18 IU/L), LH (0.54 IU/L) and E2 (16.75 pg/ml) were also noted. The serum FSH and LH levels response to 100  $\mu$ g luteinizing hormone-releasing hormone (LHRH) intravenous injection at 0, 30, 60 and 120 minute was 1.23, 2.06, 2.52, 3.04 IU/L and 0.61, 2.15, 2.87, 2.83 IU/L, respectively.



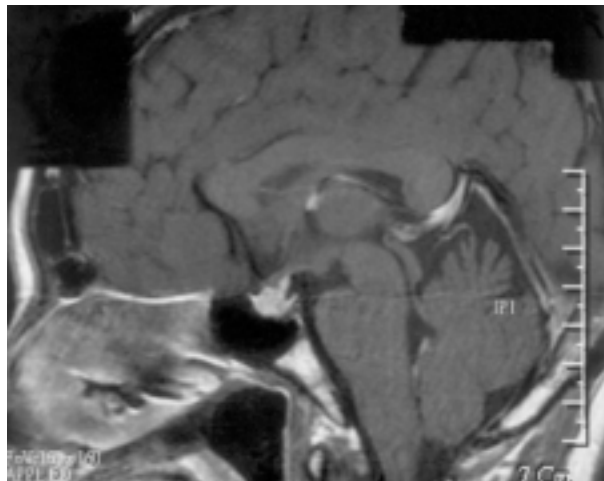
**Fig. 3A** The third T1-weighted magnetic resonance imaging (coronal view) on September 15, 2004 (eight months after delivery) revealed a mild central bulging of the pituitary gland without involving neighboring organs.

Low levels of FSH and LH, with subnormal and delayed response, were noted in the LHRH test. Hypogonadotropic hypogonadism was suspected but hypothalamus dysfunction could not be excluded. The anti-microsomal antibody and anti-thyroglobulin antibody were negative. She received cortisone acetate (25 mg in the morning and 12.5 mg in the afternoon) and Eltroxin (50  $\mu$ g per day) for hypopituitarism. She did not complain of any neurological symptoms during follow-up for half a year.

## DISCUSSION

Pregnancy or delivery related pituitary lesions might be related to such conditions as physiological enlargement of the pituitary gland during pregnancy, enlargement of a previous prolactinoma, pituitary apoplexy or hemorrhagic necrosis of an adenoma, Sheehan's syndrome and lymphocytic hypophysitis (LYH).

The size of the pituitary gland will increase 120% to 136% during pregnancy<sup>(1-4)</sup> because more estrogen stimulates hyperplasia of lactotrophs during pregnancy.<sup>(6)</sup> Lactotroph hyperplasia starts in early pregnancy and then disappears gradually within several weeks to months after the end of pregnancy (delivery or abortion).<sup>(1)</sup> The height of the pituitary gland is correlated to gestational age (0.08 mm per week)<sup>(2)</sup> but it seldom increases to more than 10 mm



**Fig. 3B** The third T1-weighted magnetic resonance imaging with contrast of Gd-DTPA (sagittal view) on September 15, 2004 (eight months after delivery) revealed a mild central bulging of the pituitary gland without filling defect.

during pregnancy.<sup>(2-4)</sup> The pituitary gland is at its largest and has marked convexity of shape in the first week of the postpartum period (few glands' height were 10-12 mm) and then it rapidly returns to normal size (2 weeks to 6 months after delivery).<sup>(1,2,4)</sup> Our patient had headaches and visual field defects in the second trimester. At that time, her pituitary gland had enlarged to more than 20 mm in height. The size was larger than that of reported physiological enlargement of pituitary glands during pregnancy. However, physiological enlargement could not explain the changing size of her pituitary gland. Also, our patient had the normal prolactin level during pregnancy and the undetectable prolactin level with inability to lactate after delivery. These clinical presentations were not compatible with prolactinoma.

LYH is a special immunological disease of the pituitary gland during pregnancy but it does not have pathognomonic clinical, radiographic or laboratory features. Its most common complications are headache and visual field impairment.<sup>(7)</sup> It can also cause several pituitary dysfunctions, and ACTH deficiency is usually the earliest and most frequent. A third of patients have hyperprolactinemia, and hypoprolactinemia is relatively rare.<sup>(7)</sup> Diabetes insipidus is also usually present.<sup>(7)</sup> The images of LYH on cranial MRI include symmetrical suprasellar expansion, thickened stalk without deviation, homogenous, isointense to brain signal intensity on T1-weighted images, isointense or hyperintense to white matter signal intensity on T2-weighted images, and homogenous or peripheral enhancement with a strip of enhanced tissue along the dura madre (the so-called "dural tail") after the administration of Gd-DTPA.<sup>(7-8)</sup> Symptoms of LYH may temporarily improve near the end of pregnancy and aggravate immediately following delivery.<sup>(9)</sup> Although LYH could not be excluded completely in our patient according to the symmetrical suprasellar expansion of the pituitary gland that remitted spontaneously, neurological symptoms and postpartum hypopituitarism, LYH could not explain why her symptoms improved dramatically after delivery. Also, the course of her pregnancy was smooth without other complications.

A large pituitary mass has higher risk of apoplexy or hemorrhage during pregnancy, and then produces a larger pituitary lesion suddenly to cause neurological symptoms or signs. Pituitary apoplexy

or hemorrhage might cause pituitary necrosis and then the size of the pituitary lesion will become smaller gradually. Hypopituitarism might also appear later. Although pituitary apoplexy was suspected initially according to our patient's clinical presentation and first MRI, her second and third MRI did not show any sign of pituitary apoplexy or hemorrhagic necrosis.

Sheehan's syndrome can cause anterior pituitary dysfunction and empty sella several years after pregnancy but does not cause a large pituitary gland. Our patient gave birth by cesarean section and had no complications during delivery. Therefore Sheehan's syndrome does not explain what happened to our patient.

Visual disturbance in pregnancy after ovulation induction has been reported in one patient. Her skull X-ray revealed new erosion of the posterior clinoid processes and loss of lamina dura of the dorsum sellae during pregnancy. The visual fields became full to confrontation after delivery.<sup>(5)</sup> However, this patient received human chorionic gonadotrophin (HCG) and human menopausal gonadotrophin (HMG), which did not stimulate the pituitary gland. In contrast, our patient received clomiphene, which stimulated the secretion of FSH.

According to the serial cranial MRI and clinical course, we have tried to explain this event. However, we could not confirm if our patient had any pathological anterior pituitary dysfunctions before pregnancy because they were not studied before pregnancy. We hypothesize that her pituitary gland became hyperplastic under ovulation induction. Pregnancy induced more enlargement of the pituitary gland, which compressed the optic chiasma, and caused her neurological symptoms in the second trimester. The large pituitary gland was more susceptible to relative ischemic change during delivery, like the mechanism of Sheehan's syndrome. As a result she had anterior pituitary dysfunctions in the postpartum period. The physiological enlargement of the pituitary gland during pregnancy remitted and the increased blood flow in the pituitary gland during pregnancy decreased greatly after delivery, so her neurological symptoms improved dramatically. We then saw a spontaneous remission of the pituitary enlargement and postpartum hypopituitarism. However, we did not obtain any pathological proof to confirm whether LYH was superimposed in this case even before pregnancy.

In conclusion, ovulation induction is safe in most infertile women but further study is needed to ascertain if clomiphene causes pituitary hyperplasia in some infertile women. When a pregnant woman has headaches and visual problems, pituitary gland lesions should be evaluated carefully. If no adequate evidence of prolactinoma, pituitary apoplexy or hemorrhagic necrosis of an adenoma is found, surgical intervention might not be necessary. Close neurological evaluations and imaging studies should be performed. These patients might avoid unnecessary surgery during pregnancy but might have a higher risk of postpartum hypopituitarism. Endocrine surveys should be performed regularly in these patients to detect hypopituitarism as early as possible.

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## 產後自發性緩解的懷孕時異常腦下垂體腫大

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誘導排卵很少造成腦下垂體異常，懷孕時腦下垂體生理性變大也很少引起症狀。此病例不孕 2 年後在誘導排卵後成功懷孕，卻在第二孕期時發生頭痛、視力模糊和視野缺損，當時的核磁共振掃描發現腦下垂體異常腫大(高 2 公分)，並壓迫到視交叉神經，這些症狀在生產後明顯改善，產後 40 天的核磁共振掃描發現腦下垂體的高度減至 1 公分，產後 8 個月更恢復到接近正常。此病例讓我們注意到懷孕時腦下垂體可能異常腫大，但是若未繼續有神經學上的惡化，宜密切追蹤觀察，有可能它自己會恢復，手術也許並不需要，但產後還需追蹤腦下垂體內分泌功能，因為有可能在產後一段時間才出現腦下垂體功能低下。(長庚醫誌 2007;30:81-6)

**關鍵詞：**腦下垂體，懷孕，淋巴球性腦垂腺炎，誘導排卵。

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