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CASE REPORT

Sustained Maintenance of Normal Insulin-like Growth Factor-I during Pregnancy and Successful Delivery in an Acromegalic Patient with Octreotide-LAR® Treatment

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We report here on a 34-year-old Korean woman with active acromegaly and who received Octreotide-LAR® for 12 months following transsphenoidal pituitary surgery. During Octreotide-LAR® treatment, the clinical improvement was paralleled with the decrease of the growth hormone levels to 1.1 ng/mL and the insulin-like growth factor-I (IGF-I) levels to 345.5 ng/mL. Octreotide-LAR® was discontinued when the patient was found to be at the 12th week of pregnancy. During pregnancy, the patient experienced clinical well-being and she maintained her IGF-I levels within the normal range for her age-matched despite discontinuation of Octreotide-LAR® treatment at early gestation. She delivered a full-term healthy male infant. The serum IGF-I levels of the patient increased progressively increased after delivery. This report describes a successful pregnancy in an acromegalic woman who was exposed to Octreotide-LAR® during the early gestational period. She and who showed an unexpected pattern of persistently normal IGF-I levels through the pregnancy despite discontinuation of Octreotide-LAR® therapy. (*Endocrinol Metab* 25:213-216, 2010)

Key Words: Acromegaly, Insulin-like growth factor-I, Octreotide, Pregnancy

INTRODUCTION

Acromegaly is an endocrine disease caused by a continuous hypersecretion of growth hormone (GH). Women with acromegaly have common symptoms of amenorrhea and infertility. Even though they become pregnant, the problem of intrauterine implantation often leads to a miscarriage in early gestation. Therefore, reports on successful pregnancy are rare. Octreotide-LAR®, a somatostatin analogue, is the established treatment in acromegaly, but it is not recommended for use in women during pregnancy because the safety of its use in pregnant women has not yet been established. Although the cases of successful delivery related to Octreotide-LAR® have recently reported [1-3], there were few reports on the sustained maintenance of normal insulin-like growth factor-I (IGF-I) levels during pregnancy and successful delivery after the Octreotide-LAR® exposure during early pregnancy [1,4,5]. This report describes a successful pregnancy in an acromegalic woman who was exposed to Octreotide-LAR® during the early gestational period and who showed an unexpected pattern of persistently normal IGF-I levels through the pregnancy despite discontinuation of Octreotide-LAR® therapy.

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CASE REPORT

A 34-year-old female patient, the mother of a 7-year-old child, had presented in 2002 with a 7-year history of amenorrhea and galactorrhea, rugged facial contour and enlarged hands and feet. The diagnosis of a GH secreting tumor was confirmed by increased serum levels of IGF-I, unsuppressed serum levels of GH after oral glucose tolerance test (OGTT) and the finding of a mass on sellar magnetic resonance imaging (MRI) (Fig. 1). IGF-I level was 859.8 ng/mL, and basal GH level was 74.2 ng/mL and rose paradoxically during OGTT (Fig. 2). In November 2002, she underwent trans-sphenoidal adenomectomy (TSA).

At 2 weeks after TSA, random GH level was 23.94 ng/mL (reference value 0.5-4.5) and IGF-I level was 925.8 ng/mL (reference

value by age: 140-405). The combined pituitary stimulation test performed at 1 week after surgery, showed normal pituitary function except for GH. Because the patient refused the injection therapy, bromocriptine treatment was initiated and continued for 10 months. Despite the treatment with bromocriptine, high serum levels of random GH and IGF-I concentration (GH: 15.20 ng/mL, IGF-I: 822.5 ng/mL) persisted even for 20 months after TSA. Therefore, bromocriptine was stopped and once monthly Octreotide-LAR® intramuscular injections were initiated in order to control active acromegaly in July 2004 (20 months after surgery). Two months later since the initiation of Octreotide-LAR®, menses resumed. During Octreotide-LAR® treatment, clinical improvement was paralleled with the decrease of random GH levels to 1.1 ng/mL and IGF-I levels to 345.5 ng/mL. But Octreotide-LAR® was discontinued at 33 months after TSA, because the patient was found to be at the 12th week of pregnancy. Other basal pituitary hormone levels were assessed at that time. The prolactin level was increased to 72.9 ng/mL. However, thyroid hormone, serum cortisol, and ACTH showed within the normal range. A 100 g oral glucose tolerance test done

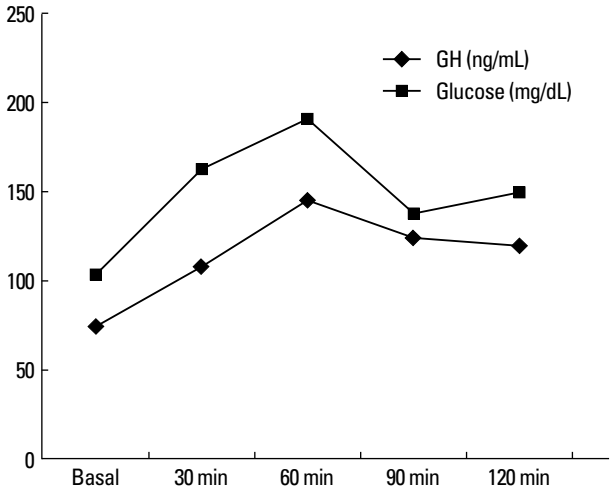

Fig. 2. Change of serum growth hormone (GH) concentration in 75 g oral glucose loading test at initial diagnosis.

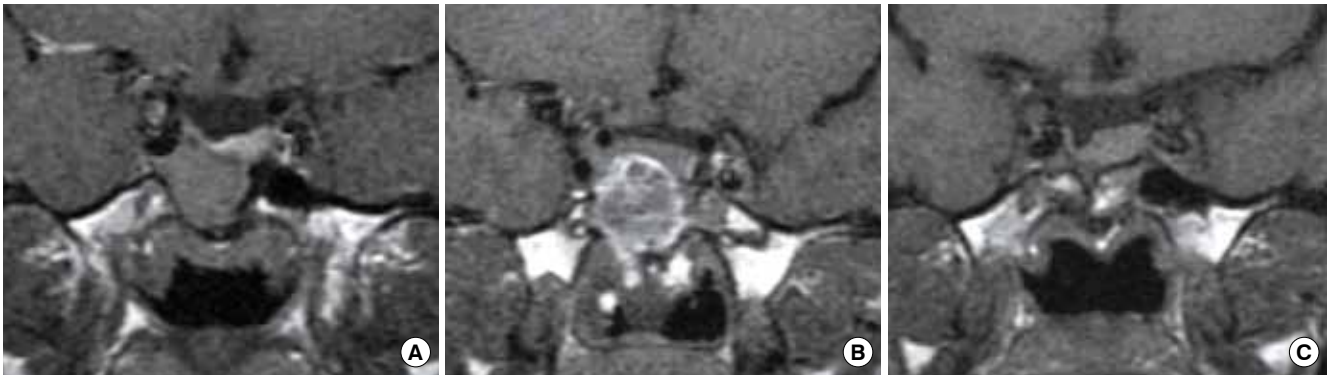

Fig. 1. Comparisons of sellar MRI performed at preoperative (A), postoperative (B) and post-delivery period (C).

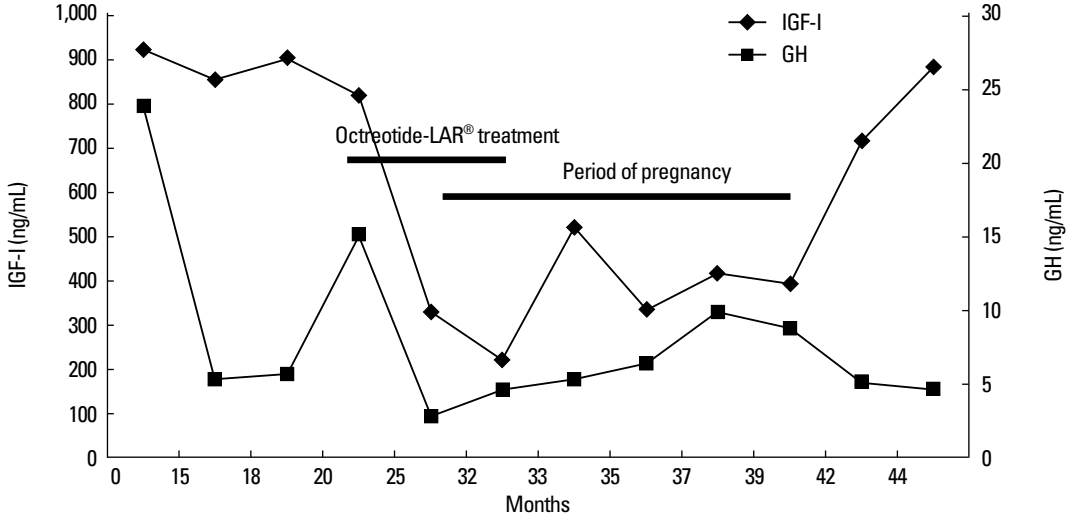

Fig. 3. Clinical course of serum levels of IGF-I and growth hormone (GH) during pregnancy and postpartum period.

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at the 28th week of pregnancy showed normal glucose tolerance and there was no decline or defect of vision during pregnancy. Prenatal ultrasonography performed by an obstetrician showed no abnormalities in the fetus. During pregnancy, she experienced clinical well-being, regression of skin thickening, reduction in size the hands and feet, and normal IGF-I levels during pregnancy (Fig. 3). She delivered a developmentally normal 2.9 kg male infant by normal vaginal delivery at the 39th week of pregnancy. The newborn infant's Apgar score was 9 at one minute and 9 at five minutes. The infant was breast-fed. The sellar MRI performed immediately after the delivery did not show any significant tumor growth or shrinkage (Fig. 1). Although serum IGF-I level and basal GH level increased progressively after delivery, she refused Octreotide-LAR® treatment because of the accelerated hair loss. At the time of 3 years after delivery and 3.5 years after stopping the treatment for acromegaly, she performed an OGTT. Basal serum GH was 5.14 ng/mL, and the nadir was 4.68 ng/mL, and serum IGF level was 781 ng/mL. Consequently, the patient agreed to resume treatment with Octreotide-LAR®.

DISCUSSION

Women with acromegaly commonly have menstrual irregularity, amenorrhea and infertility; therefore reports of pregnancy occurring in acromegalic patients are not common. Even if conception is successful, problems with intrauterine implantation often lead to miscarriage in early gestation because the physical pressure on the pituitary gland from tumor growth may bring about dysfunction of the anterior pituitary with resulting increased prolactin levels and decline in gonadotropin secretion [6-8]. Recently, cases of successful pregnancy and delivery through extended treatment with drugs and surgical intervention have been reported, and the case of successful delivery in acromegalic patient has also been reported in Korea [9].

Growth hormone physiology during pregnancy is different in normal and acromegalic patients. During the first half of normal pregnancy, GH in maternal blood is originated form pituitary. During the latter half, specific GH variant is secreted mainly from placenta in a non-episodic pattern, and serum concentration of IGF-I rises in late pregnancy, resulting in inhibition of normal pituitary GH secretion [10]. In acromegalic women, however there is persistent pituitary GH secretion throughout pregnancy [11]. Thus serum IGF-I levels in both normal and acromegalic women increase in late pregnancy [11,12].

Based on such facts, it was predicted that the IGF-I levels would be increased in late pregnancy in this patient. However, the patient's IGF-I concentration remained within the normal range from gestation to delivery. As far as we know, four acromegalic cases with similar hormonal patterns have been reported [1,4,5,13]. Three cases were women with active acromegaly despite pituitary surgery who were exposed to Octreotide treatment into early gestation only. Despite the discontinuation of Octreotide treatment, serum IGF-I levels remained unchanged during pregnancy. After delivery, the serum IGF-I levels increased again but MRI of the pituitary showed no changes in the tumors. The fourth case also showed similar endocrinologic finding, but there was no history of Octreotide treatment.

Several possible mechanisms for such a pattern are suggested. The first is due to the increase in sensitivity to Octreotide in women in early gestation, causing a prolonged effect throughout the pregnancy. However, in the case without Octreotide-LAR® there was a similar pattern and sharp increase in IGF-I after delivery [13]. The second is the surge of peripheral hormone levels in women during pregnancy caused by tumor necrosis. However, since there was no evidence of tumor necrosis on sellar MRI of the patient in this case, this explanation is less likely. A third possibility is the existence of placenta GH variants, such that certain placenta GH forms do not induce IGF-I production. But this suggestion needs to be confirmed through additional studies.

Although most accepted explanation is that IGF-I secretion is inhibited by increased estrogen concentration [14,15], this mechanism is insufficient to explain change in IGF-I levels during pregnancy because serum IGF-I levels rises in the third trimester in both normal and acromegalic pregnant women [11].

The somatostatin analogue, Octreotide-LAR® is effective for restoring normal ovulation in acromegalic patients and patients can maintain prolonged effective concentrations by an intramuscular injection of the product once a month [16]. To date, about 20 cases of successful pregnancy and delivery without fetal malformation related to somatostatin analogue have been reported worldwide [1-5,17,18].

With the exception of a few cases, the somatostatin analog was stopped during pregnancy and in all cases patient successfully maintained pregnancy and the newborns did not develop malformation or growth abnormality. Currently there are not enough data to determine whether Octreotide-LAR® cross the placenta or causes con-

genital malformation in the fetus. Caron et al. [19] suggested that the effect of Octreotide on the fetus might be negligible due to its limited simple diffusion through the placenta, and because its serum concentration in the newborn on the 40th day after the birth was too low to be measured. They also suggested the possibility of immaturity of the somatostatin receptor in newborns [20].

In this case, the patient successfully delivered a normal infant despite the exposure to Octreotide-LAR® in to early gestation. This case and previous reports infer the possibility that Octreotide-LAR® may be safe to use during pregnancy in acromegalic patient. However, more study is needed in order to elucidate the safety profile of Octreotide-LAR® use for treating acromegaly during pregnancy. More studies also should be performed to explain the mechanism of the unexpected normal IGF-I levels during pregnancy in select acromegalic women.

SUMMARY

The reports on successful pregnancy are rare in active acromegalic patients.

Octreotide-LAR® is not recommended for use during pregnancy, but the cases of successful delivery related to Octreotide-LAR® have recently reported.

We reported a 34-year-old female patient who was exposed to Octreotide-LAR® during early gestational period and showed sustained maintenance of normal IGF-I during pregnancy and subsequent rise of IGF-I level after delivery.

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