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Normal Delivery Following an Uneventful Pregnancy in a Japanese Acromegalic Patient after Discontinuation of Octreotide Long Acting Release Formulation at an Early Phase of Pregnancy

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Abstract. We report a 35-year-old woman with active acromegaly despite pituitary surgery and irradiation who received continuous octreotide LAR treatment for the control of GH excess until discovery of her pregnancy. The patient delivered a healthy boy following an uneventful pregnancy after discontinuing octreotide LAR as soon as possible at the early phase of pregnancy. Despite a substantial maternal-fetal transfer of octreotide, postnatal development was normal at 3 years of age. In almost all previously described cases, octreotide was discontinued after pregnancy was confirmed. No side-effects of mother or fetus have been reported. Octreotide treatment in pregnancy seems to be feasible and safe. Due to the still-limited number of reported cases treated with octreotide LAR, the potential benefits of octreotide LAR treatment should be weighed carefully against its possible risks.

Key words: Acromegaly, Pregnancy, Delivery, Octreotide LAR

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OCTREOTIDE is a somatostatin analogue binding to the somatostatin receptor subtypes 2 and 5. It is an established treatment option in acromegaly and in a variety of other clinical conditions such as TSH-secreting pituitary adenomas, pancreatic islet-cell tumors and carcinoid tumors [1–4]. In recent years a long-acting sustained-release formulation of octreotide (octreotide LAR) has been developed, which contains octreotide in a biodegradable polymer complex [5]. It seems to be of comparable efficacy and of good tolerability [6]. While short-acting octreotide has to be administered several times a day, the long-acting formulation needs to be injected only once every 2–4 weeks [7]. Thus, octreotide LAR provides a considerable improvement in convenience for the patient.

There is little information available on the use of octreotide in pregnancy. In fact, it has been recommended to discontinue octreotide in case of pregnancy until more safety data have been obtained [8, 9]. Here we describe the case of a pregnant Japanese acromegalic woman showing normal delivery following an uneventful pregnancy after stopping the treatment with long-acting octreotide when the early stages of pregnancy were noticed.

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Case Report

The 24-year-old patient presented with a 2-year history of headaches, and enlargement of hands and feet in September, 1990. The diagnosis of a growth hormone (GH)-secreting adenoma invading cavernous sinus was confirmed by elevated blood levels of GH (79.7 ng/ml; normal range <5 ng/ml) and somatomedin-C (10.1 U/ml; normal range 0.4–1.6 U/ml), and also by magnetic

resonance imaging (MRI). She underwent partial resection of the tumor by transsphenoidal surgery in December, 1990 followed by administration with bromocriptine because of incomplete removal of the tumor.

Although no recurrent tumor was clearly found by MRI, endocrinological data, such as GH (40.0 ng/ml) and IGF-I (937 ng/ml) levels, indicated the presence of a remaining tumor. Bromocriptine therapy was continued because of the patient's wish to have delivery, but it failed to control the serum GH level satisfactorily even at an elevated dose of 20 mg/day. Octreotide was started in August 1992, but the serum GH level was unstable because of the patient's poor compliance with the treatment regimen. She always showed normal menstrual cycle even after the transsphenoidal surgery. Octreotide was discontinued in August 1994, when the patient was found to be at the sixth week of pregnancy. She delivered the baby at another hospital in April 1995. She had no particular pregnancy-related or delivery-related problems, and the newborn was found to have no abnormalities.

With recurrent invasion found in the cavernous sinus by MRI, she was referred to our hospital again in August 1996. Blood levels of GH and IGF-I just before gamma-knife radiotherapy were 21.0 ng/ml and 786 ng/ml, respectively. Gamma-knife radiotherapy was performed for the treatment of the remaining tumor. However, with postoperative levels of GH and IGF-1 still as high as 14.4 ng/ml and 786 ng/ml, respectively, she was continuously treated with bromocriptine. Subcutaneous injection of octreotide was started in March 1997, and continuous subcutaneous injection of octreotid was started at a dose of 200 μg/day in October 1998. With concomitant use of bromocriptine, the serum GH and IGF-1 levels improved to a range of 2–5 ng/ml and around 500 ng/ml, respectively.

In May 2001, the patient began to participate in a clinical trial of octreotide LAR. Octreotide LAR was injected intramuscularly at a dose of 30 mg (the doses from the second to fifth injection were 20 mg) at four-week intervals. During the trial, the serum GH level remained around 5 ng/ml (Fig. 1), and normal menstrual cycle was observed.

On January 21, 2002, the day on which the ninth dose was given (224 days after the first dose), she was found to have been pregnant for two weeks and five days (at age 35) by the self-checking pregnancy test for her urine. She was withdrawn from treatment with octreotide LAR at this time point and remained pregnant. Without headache, impaired glucose tolerance or gynecological complications during pregnancy, she delivered a male neonate (second child) weighing 3248 g. The newborn Apgar score was 9 at 1 minute and 10 at 5 minutes, and there were no postpartum problems with the mother or the infant. The serum octreotide level was 0 pg/ml at the 26th week of pregnancy, but the serum GH and IGF-1 levels remained stable during pregnancy ranging from about 5–8 ng/ml and from about 120–200 ng/ml, respectively (Fig. 1). The GH

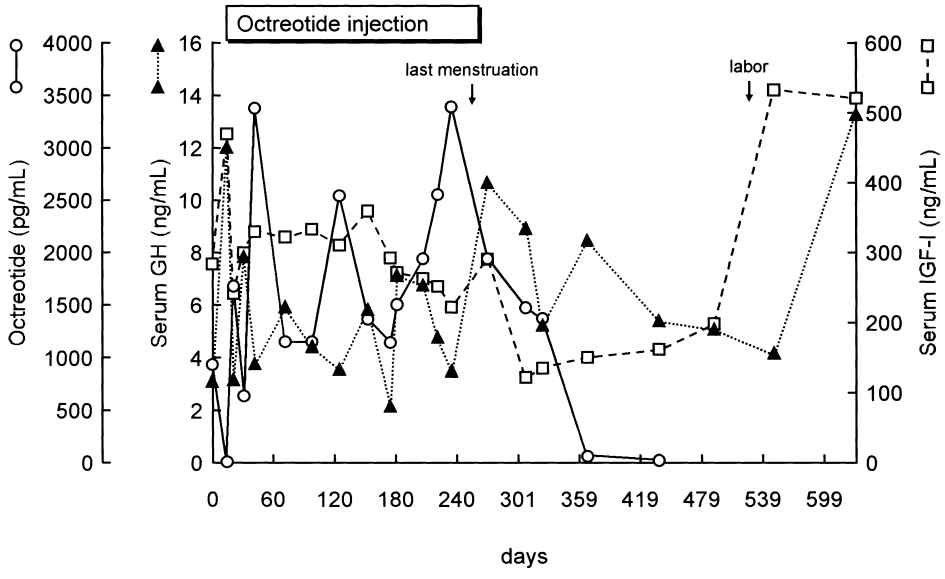

Fig. 1. Clinical course of serum levels of GH, IGF-I and octreotide concentration during pregnancy after injecting octreotide LAR.

and IGF-1 levels in the umbilical cord blood at delivery were 28.1 ng/ml and 43 ng/ml, respectively. After delivery, the serum GH and IGF-1 levels increased again, but MRI of the tumor showed no changes. Her boy is now 3.5 years old and does not have any problems in his growth and health conditions.

Discussion

In the literature, 19 cases of pregnancy have been reported in the patients with acromegaly during treatment with a somatostatin analogue (octreotide or lanreotide; octreotide LAR was used in four cases) [10–17]. In four of the 19 cases, the treatment was continued throughout pregnancy. The pregnancy outcomes were normal in all of the 19 cases except two. One of the exceptional cases was slight fetal growth retardation where the treatment (with a octreotide LAR) was continued and the other was a case of delivering an extraordinarily large newborn where the treatment had been discontinued [12]. In the former case, there was no problem with postnatal development. Maternal-fetal transfer of octreotide has been shown in patients with acromegaly or thyroid stimulating hormone-producing tumor treated with the drug, though it did not affect the blood level of thyroid stimulating hormone (TSH), thyroid hormone or IGF-1 in the newborns [11, 13, 18]. The unaffected blood TSH, thyroid hormone and IGF-1 levels in newborns are associated with incomplete somatostatin receptors in newborns [11, 18]. On the other hand, placental GH secretion is not inhibited by the administration of octreotide during pregnancy because most of the somatostatin receptors occurring on the placenta are receptor SST4, whose affinity to somatostatin is low [19]. No signs of fetal toxicity were observed in rats and rabbits receiving octreotide at the doses up to 16 times over the maximum human dose calculated based on body surface area (reproduction studies conducted by Novartis Pharma Ltd., unpublished data). It is considered that, in our present case, some remaining octreotide in the patient was transferred to the fetus in the early stages of pregnancy. However, the fact that there were no fetal complications suggests that the octreotide did not affect placental GH secretion or fetal somatostatin receptors significantly. Moreover, we discontinued to use octreotide LAR in this case as soon as possible at the early phase of pregnancy. Thus, it is suggested that octreotide LAR may be used safely, although further observations will be needed.

The present case was interesting in that the serum GH and IGF-1 levels changed differently from the patterns commonly observed during pregnancy. In both normal pregnancy and pregnancy concomitant with acromegaly, the serum GH and IGF-1 levels are known to increase over time [20]. In the latter half of normal pregnancy, the serum IGF-1 level increases with increased placental GH secretion, and pituitary GH secretion is therefore suppressed. In pregnancy concomitant with acromegaly, on the other hand, the blood IGF-1 level increases in the late stages of pregnancy but pituitary GH secretion is not suppressed [20]. In the present case, the serum GH and IGF-1 levels did not increase after the decrease and even after elimination of octreotide in blood following the discontinuation of octreotide, but increased after delivery. Another case with the same endocrinological pattern [16] and other cases with similar endocrinological patterns [10, 14] have also been reported. As possible mechanisms to explain this phenomenon, IGF-1 production reduced by increased estrogen levels, enhanced sensitivity to octreotide and thus prolonged effect of octreotide, and, alternatively, a tumor infarction following the stimulation by peripheral hormone surges during pregnancy have been mentioned [10]. In our case, the serum GH level remained low until delivery without signs of a tumor infarction, and the serum octreotide level became undetectable at the 26th week of pregnancy. We therefore could not elucidate the mechanism of this endocrinological pattern. A case has also been reported where unusual endocrinological changes were observed in an acromegalic woman who was not treated with a somatostatin analogue during pregnancy [21]. From the facts aforementioned, further investigation is considered necessary to elucidate the characteristics of endocrinological functions in pregnant women with acromegaly treated with a somatostatin analogue.

In conclusion, we experienced a case of acromegaly where the patient became pregnant during treatment with octreotide LAR and had delivery. There were no clinical problems with pregnancy, delivery and the newborn after discontinuation of octreotide LAR treatment at the early stages of pregnancy. The cases reported previously also suggest the safety of octreotide during pregnancy. However, experience with the use of octreotide during pregnancy is still limited and therefore further cases need to be accumulated.

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