A Case of Active Acromegalic Woman with a Marked Increase in Serum Insulin-like Growth Factor-1 Levels after Delivery

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Abstract. Pregnancy in a woman with active acromegaly is very rare, because amenorrhea, due to hyperprolactinemia and disturbed pituitary gonadotropin secretion may cause infertility. We report a 28-year-old pregnant woman with untreated acromegaly, who was followed up from early pregnancy to delivery. Her pregnancy was uneventful, and she went into spontaneous labor at 38 weeks and delivered a normal infant. Her serum GH levels were further increased in late pregnancy, followed by decreased in postpartum periods, which may be associated with enlargement of pituitary adenoma during pregnancy. In contrast with serum GH, her serum insulin-like growth factor-1 (IGF-1) levels were dissociated with her serum GH levels during late pregnant and postpartum period. Her serum GH and IGF-1 levels in late pregnancy were different from the levels in pregnant women with acromegaly reported previously.

Key words: Acromegaly, Pregnancy, GH, Insulin-like growth factor-1 (IGF-1)

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ACROMEGALY rarely occurs in women of childbearing age. Moreover, fertility is low in acromegalic women because of amenorrhea, due to a decreased gonadotropin reserve caused by the tumor mass and hyperprolactinemia observed in 30 to 40% of them. For these reasons, there are not enough data to evaluate the outcome of pregnancy or a risk of pregnancy in acromegaly. In normal pregnancy insulin-like growth factor-1 (IGF-1) originating in a placental GH variant is increased in late pregnancy, resulting in the suppression of pituitary GH secretion, but, in previous studies of

pregnant women with acromegaly [1], GH secretion from adenomatous somatotrophs remained high during the third trimester of pregnancy despite a rise in serum IGF-1 derived from the placenta. Here we report a pregnant woman with untreated acromegaly who showed dissociated serum levels of GH and IGF-1 in late pregnancy.

Case Report

A 28-year-old nulliparous woman first visited the department of obstetrics because of infertility 2 months before and was referred to our clinic because of acromegalic characteristics and high blood glucose (246 mg/dl). Her menarche was at age 13, and since then her menstrual cycles had been regular. At 20 years of age she became aware of an enlargement of her nose, lips and extremities and a widening of spaces between her teeth. She

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had been infertile for 2 years despite a regular menstrual cycle. Physical examination revealed that her height was 171 cm and weight was 79 kg. She had acromegalic characteristics associated with deepening of voice, coarse skin, soft tissue hypertrophy, thickened digitus and extremities, and prognathism. No abnormal findings were observed on ophthalmologic examination including optic fundi, visual acuity and visual field. Her fasting plasma glucose was 124 mg/dl. Hemoglobin A_{1c} (HbA_{1c}) was 7.4 % (normal: 4.0–6.0%) and urinary C-peptide was 209.7 μ g/day (normal: 16–120 μ g/day). Serum GH measured with a two-site immunoradiometric assay kit using two different monoclonal antibodies (Daiichi Radioisotope Labs., Ltd, Tokyo, Japan) was 21.9 ng/ml (normal: 0.66–3.8 ng/ml). The antibodies used in the kit did not crossreact with placental GH or placental lactogen. Serum IGF-1 measured with an immunoradiometric assay kit (Chiba Corning Labs., Ltd, Tokyo, Japan) after the extraction of serum by ethanol was 828 ng/ml (normal female: 121–436 ng/ml). On the other hand, serum IGF-binding protein-3 (IGFBP-3) measured by an immunometric assay kit (Diagnostic Systems Laboratories Inc, Webster, Texas, USA) was 6.9 μ g/ml (normal females: 3.2–4.2 μ g/ml). A paradoxical increase in serum GH was observed in the 75 g oral glucose tolerance test (33.3 to 52.9 ng/ml). Serum GH levels were also increased from 22.7 to 107.1 ng/ml and from 30.5 to 48.7 ng/ml by the iv administration of LH-RH (100 μ g) and TRH (500 μ g), respectively. The secretion of other anterior pituitary hormones, including PRL, was normal. The administration of bromocriptine (2.5 mg) suppressed her serum PRL levels, but not serum GH. A brain magnetic resonance imaging (MRI) revealed that she had a 10 mm pituitary adenoma and no evidence of suprasellar extension (Fig. 1A). When she was diagnosed as having acromegaly due to a pituitary GH secreting tumor, she was 8 weeks pregnant. As she and her husband strongly wished to have the baby, regardless of the hazards, she was followed up without any medication.

Her diabetes mellitus was controlled by a 1800 Kcal diet in the first trimester, and then followed up with 2000 Kcal in the second trimester and 2200 Kcal in the third trimester. Her fasting blood glucose levels were 100–120 mg/dl, and her HbA_{1c}

Fig. 1. A: A brain MRI revealed that she had a 10 mm size of pituitary microadenoma and no evidence of suprasellar extension at 8 weeks of gestation. B: A brain MRI revealed a suprasellar extension of her pituitary tumor at 34 weeks of gestation.

values were 6.0–6.4% during the gestational period. At 38 weeks she went into spontaneous labor and delivered a normal female infant (weight: 2882 g) without any complications.

Her serum GH levels were maintained at 20.0–28.8 ng/ml until 31 weeks of gestation, and were increased to 92.8 ng/ml and 74.4 ng/ml at 35 and

Table 1. Serum GH, IGF-1, estradiol during pregnancy and postpartum in an acromegalic patient

		Pregnant period (weeks)					Delivery	Post partum period (weeks)	
		8	24	31	35	38	↓	1	2
GH	(ng/ml)	28.8	25.2	25.3	92.8	74.4		28.2	26.3
IGF-1	(ng/ml)	828	855	655	817	553		1580	1750<
E ₂	(pg/ml)	320	8300			28000		130	64
IGFBP-3	(μg/ml)	6.9	8.5	5.7	8.3	6.2		5.4	

IGF-1, insulin-like growth factor-1; E₂, estradiol; IGFBP-3, IGF-binding protein-3.

38 weeks (just before delivery), respectively (Table 1). The levels decreased rapidly after delivery and were 28.2 and 26.3 ng/ml at 1 and 2 weeks postpartum, respectively. Serum IGF-1 levels were 553–855 ng/ml during the pregnancy. In contrast with the serum GH levels, the serum IGF-1 levels rose to 1530 and more than 1750 ng/ml at 1 and 2 weeks after delivery. We also carefully checked concerning about pituitary apoplexy with the tumor expansion in pregnancy. A brain MRI was carried out at 8, 20 and 34 (Fig. 1B) weeks of gestation and at 4 weeks after delivery. The MRI revealed a suprasellar extension of her pituitary tumor in the third trimester, but she did not have any abnormality of the visual field. Her pituitary tumor at 6 months after delivery was smaller than at 4 weeks after delivery. She was operated on by transsphenoidal approach 6 months after delivery, and her serum GH and IGF-1 levels were 0.1 ng/ml and 80 ng/ml, respectively, at 6 months in the follow-up period.

Discussion

This acromegalic woman had a 2-year history of infertility despite preserved gonadotropin secretion and normal serum PRL levels, but pregnancy was unexpected when she was diagnosed as having acromegaly in our clinic. Her pregnancy was uneventful and no complications were observed during pregnancy, despite the further enlargement of her pituitary adenoma in the third trimester. Unsolved problems are the outcome of a pregnancy and the risk of complications developing during pregnancy in acromegalic women. A mild acromegalic state does not appear to be an obstacle to a normal pregnancy [2]. This patient with a GH

secreting adenoma did not have any complications during pregnancy despite the enlargement of her pituitary adenoma associated with an increase in serum GH levels during late gestation. Indications for surgery during pregnancy are not clear, though patients who have undergone hypophysectomy during gestation have maintained an uneventful pregnancy [3].

It is well established that during the second half of a normal pregnancy, the human placenta secretes its specific GH variant and IGF-1 in increasing amounts up to delivery and the serum concentration of IGF-1 rises in late pregnancy, resulting in the inhibition of normal pituitary GH secretion [4, 5]. Becker *et al.* reported two pregnant women with acromegaly whose pituitary GH secretion remained high during the entire pregnancy, whereas serum IGF-1 levels rose in late pregnancy [1]. They hypothesized that in acromegalic women, placental GH is the main stimulator of IGF-1 secretion in late pregnancy and adenomatous somatotrophs lack an IGF-1 dependent negative regulatory mechanism. Nevertheless, it is to be noted concerning our acromegalic patient that serum IGF-1 levels fell in late pregnancy in contrast with her first trimester, and her serum GH levels rose. After delivery, serum GH levels rapidly returned to the former levels and IGF-1 levels rose noticeably. In this patient, the oversecretion of GH in late pregnancy may be associated with the enlargement of the pituitary tumor. Estrogens also exert their stimulatory effect on GH secretion directly on the pituitary [6, 7]. On the other hand, the administration of estrogens to acromegalic patients causes a reduction of serum IGF-1 (somatomedin-C) bioactivities and serum IGF-1 concentrations without consistent changes in serum GH levels,

which results in an improvement in the clinical status and biochemical abnormalities [8]. In this patient serum estrogen levels may associate with the oversecretion of GH from adenomatous somatotrophs in late pregnancy and with a marked increase in serum IGF-1 levels in postpartum period. But the oversecretion of estrogen cannot account for the reduction in serum IGF-1 levels in late pregnancy, because serum IGF-1 levels in the third trimester rise in both normal and acromegalic

pregnant women [1]. We could not explain the changes in serum IGF-1 during the late pregnant and postpartum periods in this patient.

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