Case Report
DOI: 10.25179/tjem.2017-56497
Turk J Endocrinol Metab 2017;21:136-139

Acromegaly and Pregnancy: Five New Cases

Akromegali ve Gebelik: Beş Yeni Vaka

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Abstract

Pregnancy is a rare occurrence in acromegalic patients because of impaired fertility due to the disease. There are limited data available regarding pregnancy in acromegalic patients; although, it appears that the patients are usually able to carry their pregnancies to full term. In addition, certain metabolic effects of acromegaly need to be considered as they can be harmful to both mother and fetus. The discontinuation of the medical treatment is usually recommended as the effects of medical treatment are unclear. Herein, we report five new cases of pregnancies in acromegalic patients who had undergone surgery and medical treatment for macroadenoma, before the onset of pregnancy, from different centers. Two of them had received radiotherapy after the surgery. None of the patients in our study were treated for pregnancy; however, two of them were receiving octreotide when the diagnosis of pregnancy was established. The medical treatment of these two patients was discontinued at the beginning of pregnancy. Four patients delivered healthy babies, and therapeutic abortion was performed at the sixth week of pregnancy to one of the patients who was being treated with octreotide before the pregnancy. Out of the five patients in our study, two had pregestational diabetes and one had hypertension. As a conclusion, it can be said that pregnancy in acromegalic patients is usually uneventful without any treatment throughout the pregnancy.
Keywords: Acromegaly; pregnancy; medical therapy

Özet

Gebelik, akromegalik hastalarda bozulmuş fertilite nedeni ile nadir görülür. Gebelik sırasında akromegaliye yaklaşım konusunda sınırlı sayıda veri olmasına rağmen genellikle hastaların gebeliklerinin term doğumla sonuçlandığı görülmektedir. Ek olarak akromegalinin farklı metabolik etkileri, anne ve fetusa zarar verebileceğinden, göz önünde bulundurulmalıdır. Medikal tedavinin etkileri net olmadığından sıklıkla tedavinin kesilmesi önerilir. Burada farklı merkezlerden elde edilen veriler ile gebelik öncesi makroadenom nedeni ile cerrahi ve medikal tedavi uygulanmış 5 akromegalik hastada yeni gebelik vakaları sunduk. Bunlardan iki hastaya operasyon sonrası radyoterapi uygulanmıştı. Hastalarımızdan hiçbirine gebelik için tedavi uygulanmamıştı, fakat iki tanesi gebelik saptandığında oktreotid tedavisi almaktaydı. Bu iki hastanın medikal tedavisi gebelik başlangıcında kesildi. Dört hasta sağlıklı bebekler doğurdu ve oktreotid tedavisi alan hastalardan birine altıncı haftada terapötik abortus uygulandı. Beş hastamızdan iki tanesinde pregestasyonel diyabet, bir tanesinde ayrıca hipertansiyon saptandı. Sonuç olarak akromegalik gebelerde hiçbir medikal tedavi uygulanmaksızın komplikasyonsuz gebelik gerçekleşebileceği söylenebilir.
Anahtar kelimeler: Akromegali; gebelik; medikal tedavi

Introduction

Acromegaly is a rarely occurring disease that is caused due to excessive secretion of the growth hormone (GH), usually by a benign pituitary tumor. Fertility is commonly impaired in the patients with acromegaly as a result of the following: hypopituitarism and a reduced gonadotropin reserve, either due to the destruction of gonadotropic cells or due to the compression of gonadotropic cells and the pituitary stalk, which results in hypothalamic-pituitary-ovarian axis dysfunction; co-secretion of prolactin and growth hormone by a mixed GH-prolactin (PRL) adenoma; or excessive GH/insulin-like growth factor 1 (IGF-1) secretion, sensitizing the ovaries to gonadotropin stimulation (1, 2).

Multiple treatment options are available for acromegaly, including surgery, radiotherapy and medical treatment. Pregnancy in acromegalic patients will become more frequent with the improvement in treatment modalities. There are limited data available regarding the pregnancies in acromegalic patients; although,

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it appears that the patients are usually able to carry their pregnancies to full term. On the other hand, the reported data have revealed that GH-secreting tumors may enlarge symptomatically during pregnancy (3). In addition, GH and IGF-1 levels change controversially during the pregnancy; however, in the majority of the cases, tumor growth is not observed (3-6).

Certain metabolic effects of acromegaly, such as diabetes mellitus and hypertension due to the elevated levels of GH and IGF-1, need to be considered as they can be harmful to both mother and fetus. Limited data are available regarding the management of acromegaly during pregnancy. Therefore, the effects of medical treatment are unclear. Here, we report five new cases of pregnancies in acromegalic patients and share our observations regarding pregnancy in acromegalic patients.

Case Reports

Case 1

A 28-year-old female patient was diagnosed with acromegaly at age 22. She underwent transsphenoidal surgery for macroadenoma three times and received postoperative pituitary gamma knife radiotherapy. She was treated with octreotide and cabergoline. Six years later, she became pregnant. Her treatment drugs were then discontinued. She did not receive any treatment for pregnancy. In her obstetric history, there had been a live birth. In addition, she had been diagnosed with diabetes mellitus and hypothyroidism in her past medical history. Before pregnancy, her serum GH was 4.26 ng/mL, and IGF-1 was 472 ng/mL (normal range: 117-329 ng/mL). She had pregestational diabetes; however, she did not develop arterial hypertension and visual field abnormality during the pregnancy. She delivered a normal, healthy infant by cesarean section at 38 weeks of pregnancy. The weight of the baby was 3.1 kg, and he did not have any congenital anomaly. Postpartum first-month GH and IGF-1 levels were 1.67 ng/mL and 381 ng/mL, respectively.

Case 2

A 31-year-old female patient was operated by transsphenoidal approach for a macroadenoma that measured 32 mm in diameter, four years ago. She received octreotide and cabergoline. She had a diagnosis of pregnancy, following which the medical treatment for acromegaly was discontinued. She did not receive any treatment for pregnancy. Before pregnancy, the serum GH level was 3.58 ng/mL, and the IGF-1 level was 370 ng/mL (normal range: 117-329 ng/mL). At 11, 22 and 30 weeks of pregnancy, the GH levels were 3.71, 3.36 and 3.09 ng/mL, respectively; and the IGF-1 levels were 240, 165 and 165 ng/mL, respectively. Her pregnancy was uncomplicated. She did not develop hypertension or gestational diabetes, and her visual field examination results were normal. She delivered a normal, full-term infant by cesarean section. The baby was healthy and her weight was 2.9 kg.

Case 3

A 40-year-old female patient, who had previously given birth to three healthy children, was diagnosed with acromegaly five years ago. She underwent transsphenoidal resection of macroadenoma twice; the first surgery was performed in 2009, and the second one in 2011. Pituitary magnetic resonance imaging (MRI) revealed a recurrent adenoma, 12x10x10 millimeter in size. She received postoperative gamma knife radiation. She also received lanreotide and cabergoline. She was diagnosed with pregnancy without any treatment and the drugs were discontinued. The mean serum-GH level was 8.01 ng/mL, and the mean IGF-1 level was 279 ng/mL (normal range: 117-329 ng/mL), between 32 and 36 weeks of pregnancy. She had been diagnosed with diabetes mellitus, hypertension, and hypothyroidism in her past medical history. She had pregestational diabetes and her visual field examination results were normal throughout the pregnancy. She underwent a cesarean section at 37.5 weeks of pregnancy and delivered a healthy, 2.9 kg baby. Postpartum first-month GH and IGF-1 levels were 28.5 ng/mL and 1380 ng/mL, respectively. MRI revealed a recurrent adenoma, 14x11x10 millimeter in size.

Case 4

A 43-year-old female patient, the mother of two children, was diagnosed with acromegaly at age 38. A pituitary MRI revealed a macroadenoma, 11x10 millimeter in size. She underwent transsphenoidal surgery. Octreotide was prescribed to her as the medical treatment for acromegaly. Postoperative MRI revealed a residual adenoma, 6 4 millimeter in size. She became pregnant and her medical treatment was discontinued. Before pregnancy, the serum GH level was 0.4 ng/mL, and the IGF-1 level was 100 ng/mL (normal range: 117-329 ng/mL). In the sixth week of pregnancy, therapeutic abortion was performed to the patient with her consent.

Case 5

A 28-year-old female patient was diagnosed with acromegaly, and adenoidectomy was performed for a 14x10 millimeter macroadenoma by the transsphenoidal approach, four years ago. After the surgery, she was treated with octreotide, at a dose of 10 mg. She became pregnant while she was being treated with octreotide. She did not receive any treatment for pregnancy and octreotide was discontinued for the rest of the pregnancy. Before pregnancy, the serum GH level was 9.3 ng/mL, and the IGF-1 level was 177 ng/mL (normal range: 117-329 ng/mL). At six months of pregnancy, the serum GH level was 3 ng/mL, and the IGF-1 concentration was 265 ng/mL. The pregnancy period was uneventful and the patient did not develop arterial hypertension or glucose abnormalities. Her visual field examination results were also normal. She delivered, vaginally, a normal, healthy, full-term infant at 40 weeks of pregnancy. The weight of the baby was 3.2 kg and he did not have any congenital anomaly.

Discussion

The retrospective study of five women, who underwent surgery and the treatment for macroadenoma from different centers before pregnancy, allowed us to analyze maternal outcomes in acromegalic patients. These five women, who were followed for a mean duration of five years, were aged between 28 and 43 years. Only two of them had received radiotherapy after the surgery.

None of these five patients were treated for pregnancy; however, two of them were receiving octreotide while they received the di-

agnosis of pregnancy. If the tumor mass or the treatments do not destroy the gonadotropin lineage, the reproductive potential is preserved; however, fertility in patients with acromegaly is generally known to be impaired (7). Conceptions (spontaneous as well as induced) have been reported in less than 150 cases in the literature till date, achieved with and without treatment (4, 5, 7, 8).

GH and IGF-1 levels were not measured routinely in the patients in our study. Maternal GH was obtained from pituitary as well as placenta during the pregnancy, depending on the trimester. The placental GH binds to GH receptors and acts as a GH agonist. The increase in the IGF-1 levels due to placental GH secretion appears to result in a negative feedback to the hypothalamus and pituitary during normal pregnancy, causing suppression of pituitary GH secretion. Nevertheless, in acromegalic patients, this feedback inhibition is rendered ineffective and the pituitary GH secretion persists throughout the pregnancy (9).

Even though the additional placental GH is present during the pregnancy, a reduction in the IGF-1 levels during pregnancy in the patients with acromegaly is usually seen even without medical treatment (7, 10, 11). It has been presumed that this improvement in the IGF-1 levels could be due to the effect of the marked increase in the estrogen levels during pregnancy (12). However, the impact of pregnancy on the GH and IGF-1 levels in acromegalic patients is limited to sporadic cases (3, 7, 13, 14). Therefore, monitoring of GH and IGF-1 levels in the pregnant acromegalic patients is not necessary.

A major concern during pregnancy in acromegalics is the tumor growth. Although theoretically, adenoma enlargement may be expected in the acromegalic patients because of the estrogen exposure (3), in the majority of the patients, tumor enlargement is not observed (4, 5, 7, 13, 15). In a normal pregnancy, this has little clinical significance; however, in patients with residual tumor or unresected tumors, an increase in the gland size can cause visual field defects, headaches, and potentially, pituitary apoplexy (16-18). In the five cases mentioned here, we did not observe any visual field impairment, pituitary apoplexy, or exacerbation of acromegaly during pregnancy; although, a routine visual field examination was not performed during the pregnancy period.

There are limited data regarding the medical treatment of acromegaly during pregnancy. In a study by Cheng et al., dopamine agonists (DA) and somatostatin analogs (SA) appear to exhibit a reduced incidence of side effects in the mothers and the fetuses (5). In addition, pregnancies have been reported to be uneventful in the acromegalic women treated with dopamine agonists, as observed in a much larger number of women with prolactinomas (13). However, since both bromocriptine and cabergoline can cross the placenta, it has been recommended to limit their usage throughout pregnancy (19).

Although SA, octreotide, and lanreotide are more efficacious than DA for the treatment of acromegaly, these agents have not been commonly used during pregnancy (4). Uneventful pregnancies have been reported in which SA was continued during the pregnancy without any side effects (13, 20, 21). Besides, medical treatment with SA during pregnancy was associated with low birth weight. It has been reported that octreotide crosses placenta (21, 22), and therefore, it may potentially affect the fetal outcome. Nevertheless, based on the lack of sufficient data on the safety of SAs during pregnancy, it is generally recommended to limit their usage during pregnancy in symptomatic patients (4). None of the five patients in our study were treated during pregnancy; while only two of them were receiving octreotide when they received the diagnosis of pregnancy, following which their medical treatment was discontinued. Out of the five pregnancies mentioned in this study, four delivered normal, full-term babies; and the therapeutic abortion was performed at the sixth week of pregnancy, to the patient who received octreotide before the pregnancy (Table 1).

Another important concern during pregnancy in patients with acromegaly is the effect of excess GH/IGF-1 levels on the mother and the fetus. Further, theoretically, women with acromegaly are at

Table 1. Demographic results of acromegalic patients who got pregnant.

	Patient 1 (H.Z)	Patient 2 (S.A)	Patient 3 (N.Y)	Patient 4 (B.T)	Patient 5 (S.A)
Age (years)	28	31	40	43	28
Duration of acromegaly	six years	four years	five years	five years	four years
Adenoma type before surgery	Macroadenoma	Macroadenoma	Macroadenoma	Macroadenoma	Macroadenoma
Radiotherapy	Gamma knife	No	Gamma knife	No	No
Medical treatment before pregnancy	Octreotide Cabergoline	Octreotide Cabergoline	Lanreotide Cabergoline	Octreotide	Octreotide
Treatment for pregnancy	No	No	No	No	No
Treatment during pregnancy	No	No	No	Octreotide 10 mg*	Octreotide 10 mg**
Gestational diabetes during pregnancy	Pregestational diabetes	No	Pregestational diabetes	No	No
Gestational hypertension during pregnancy	No	No	Yes	No	No
Gestational age/Type of delivery	38. weeks C/S	38. weeks C/S	37. weeks C/S	6. weeks curettage	40. weeks
Birth weight	3100 gram	2900 gram	2900 gram	-	3200 gram
Congenital anomaly	No	No	No	-	No

* Therapeutic abortion was performed to a patient with her wish who received octreotide before the pregnancy

** Patient received octreotide before pregnancy, the drug was stopped when the patient was found to be pregnant.

a higher risk for glucose intolerance or hyperglycemia as the pregnancy itself is an insulin-resistant state (13). Despite the limited data, the follow-up to check for the occurrence of gestational diabetes, coronary artery disease, hypertension, and dyslipidemia is strongly recommended (16, 23, 24). Acromegaly can potentially affect the fetus; however, there are limited data supporting this, as most of the studies have reported normal, healthy infants. (3, 7, 13). It is known that the disease can be associated with miscarriage, premature births, abnormal birth weight, and growth retardation (21). Among the five patients in our study, two had pregestational diabetes; one of them had hypertension and had been diagnosed with diabetes and hypertension in her past medical history. Four patients in our study delivered healthy, full-term infants; and therapeutic abortion was performed to one of the five patients.

In conclusion, according to our results together with the limited data, acromegalic female patients can conceive without receiving any treatment for pregnancy, even after treating acromegaly with surgery, radiotherapy, and medical treatment. Most pregnancies in the acromegalic patients are uneventful and the infants remain unaffected. Somatostatin analogs have been reported to be safe for usage throughout the pregnancy; however, further studies are needed to establish their safety.

Author Contributions

Concept: Elif Önder, Yusuf Aydın, Tuba Soysal. Design: Yusuf Aydın, Tuba Soysal. Data Collection or Processing: Elif Önder, Yusuf Aydın, Mazhar Tuna, Adem Güngör. Analysis or Interpretation: Yusuf Aydın, Tuba Soysal, Elif Önder. Literature Search: Yusuf Aydın, Tuba Soysal. Writing: Tuba Soysal, Yusuf Aydın.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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