Two successful pregnancies in a woman with active acromegaly

Przebieg dwóch ciąż u pacjentki z aktywną akromegalią

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KEY WORDS:

- acromegaly
- pituitary adenoma
- pregnancy
- insulin-like growth factor 1
- growth hormone

ABSTRACT

Acromegaly is a rare systemic disease, predominantly caused by growth hormone (GH)-secreting pituitary adenoma, leading to insulin-like growth factor-1 (IGF-1) overproduction. Pituitary adenoma extension and/or its treatment can cause infertility or subfertility in both sexes in different mechanisms. Pregnancies in women with active acromegaly are rarely observed but considered generally safe. Growth hormone and IGF-1 concentrations are usually stable during pregnancy and in most cases no significant tumour expansion emerges despite pharmacological therapy withdrawal.

A 28 year-old woman with symptoms of acromegaly and amenorrhoea was admitted to the Department of Endocrinology. Diagnosis of acromegaly was made and treatment with somatostatin analogues (SSA) was initiated with subsequent surgical intervention. However, persistent acromegaly was diagnosed post-operatively due to residual tumour and the medical treatment was restarted. During follow-up the patient became pregnant twice and then treatment with somatostatin analogues was ceased. Both pregnancies were complicated by gestational diabetes and in the course of the second pregnancy treatment with dopamine agonist (DA) was commenced to alleviate persistent headaches and it was followed by clinical and biochemical improvement. The patient successfully delivered two healthy babies. After second labour treatment with SSA was resumed and the patient has achieved adequate disease control.

The risk of pregnancy complications in women with acromegaly is slightly higher than in general population, especially if uncontrolled disease was present before conception or acromegaly was diagnosed during pregnancy. In rare cases pituitary tumour expansion during pregnancy occurs and then pharmacological or surgical interventions should be considered.

SŁOWA KLUCZOWE:

- akromegalia
- gruczolak przysadki
- ciąża
- insulinopodobny czynnik wzrostu 1
- hormon wzrostu

STRESZCZENIE

Akromegalia jest rzadką chorobą wywołaną nadmiernym wydzielaniem hormonu wzrostu (GH), najczęściej przez gruczolak przysadki, co w konsekwencji prowadzi do nadprodukcji insulinopodobnego czynnika wzrostu 1 (IGF-1), zmian wyglądu i licznych powikłań układowych. Rozrost gruczolaka przysadki i/lub jego leczenie może prowadzić w różnych mechanizmach do niepłodność u pacjentów obu płci. Ciąża w aktywnej akromegalii jest rzadko obserwowana, ale zazwyczaj przebiega bez powikłań. Podczas ciąży stężenia GH i IGF-1 są zwykle stabilne i w większości przypadków nie obserwuje się rozrostu gruczolaka przysadki, pomimo przerwania farmakoterapii.

28-letnia kobieta została przyjęta do Kliniki Endokrynologii z powodu objawów akromegalii i braku miesiączki. Badania hormonalne potwierdziły rozpoznanie akromegalii. Włączono leczenie analogiem somatostatyny (SSA) oraz zakwalifikowano pacjentkę do leczenia chirurgicznego guza przysadki. Po zabiegu operacyjnym stwierdzono utrzymującą się aktywną chorobę spowodowaną resztkową masą guza, wobec czego wznowiono leczenie SSA. W trakcie kilkuletniej obserwacji pacjentka dwukrotnie zaszła w ciążę. W obydwu przypadkach, po potwierdzeniu ciąży przerwano leczenie farmakologiczne SSA. Przebieg obu ciąż był powikłany cukrzycą ciążową. Ponadto, w drugiej ciąży, z powodu utrzymujących się bólów głowy, do leczenia włączono agonistę dopaminy, uzyskując kliniczną i biochemiczną poprawę. Pacjentka urodziła dwoje zdrowych dzieci. Po drugim porodzie powrócono do leczenia SSA, uzyskując kontrolę choroby.

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Ryzyko powikłań ciążowych u pacjentek z akromegalią jest nieznacznie wyższe niż w populacji ogólnej, zwłaszcza w przypadkach braku kontroli choroby przed ciążą lub rozpoznania akromegalii w czasie ciąży. W rzadkich sytuacjach wzrostu guza podczas ciąży, z objawami ucisku skrzyżowania wzrokowego lub bólami głowy, należy rozważyć interwencję farmakologiczną lub chirurgiczną.

Introduction

Acromegaly is a rare disease caused by GH-secreting pituitary adenoma. Infertility among women with acromegaly is common due to hyperprolactinaemia or gonadotrophin deficiency. However, appropriate treatment that improve fertility became available and widely applied. Thus, it is reasonable to expect an increase in the number of pregnant women with acromegaly in the future.

Case Report

A 28-year-old woman presented to the Department of Endocrinology with amenorrhea and signs and symptoms of acromegaly (enlargement of hands and feet, coarsening of facial features). No visual impairment or headache were present. Prior to admission the patient had been treated for 6 months by a gynaecologist with cabergoline due to hyperprolactinaemia. Despite treatment with dopamine agonist amenorrhoea persisted.

Hormonal tests at the Department revealed increased IGF-1 concentration (IGF-1: 701.1 ng/mL; that was IGF-1: 2.4 x upper limit of normal (ULN) for age- and gender- specific reference range: 118-294 ng/mL) and lack of suppression of GH to less than 1.0 ng/ml during oral glucose tolerance test (OGTT) (Table 1.). The results confirmed diagnosis of acromegaly. Additionally, impaired fasting glucose, hyperinsulinaemia and insulin resistance were diagnosed and treatment with metformin was initiated (Table 1.). Besides, anterior pituitary function was intact and prolactin level normalised during DA treatment. Magnetic resonance imaging (MRI) of the pituitary showed a 19 x 25 x 24 mm sellar mass with left cavernous sinus invasion and suprasellar extension.

Table 1. Results of oral glucose tolerance test (OGTT).

	GH (ug/l)	Glukoza (mg/dl)	Insulina (ulU/ml)
0 min	6.2	109	32.1
60 min	3.24	199	>300
120 min	3.31	128	>300

Source: own study.

No optic chiasm compression was evident (Fig. 1) and visual field tests did not show any impairment. The patient received long-acting lanreotide therapy and was referred for surgery. In the course of SSA treatment GH and IGF-1 concentrations normalized and the normal menstrual cycles returned. The patient underwent transsphenoidal surgery 4 months after starting SSA. Histopathological and immunohistochemical analyses of resected tumour showed densely granulated adenoma stained positively for GH and somatostatin receptors (SSTR2A and SSTR5) expression and Ki-67 <1%. However, post-operatively biochemical control was not achieved and MRI imaging confirmed a tumour remnant in the left cavernous sinus (Fig 2.). Long-acting somatostatin analogue was reintroduced and optimal biochemical control soon followed. The prevalence of gallstones is increased in acromegaly during SSA therapy. However, we did not observe cholelithiasis or any other side effect of this treatment in our patient.

When five months after surgery pregnancy was confirmed, it was decided to discontinue lanreotide therapy and the patient remained under rigorous doctor's supervision. The woman was clinically asymptomatic throughout the pregnancy. Her IGF-1 levels remained slightly above the ULN, lower than her post-operative values, with the lowest concentrations in the first trimester and highest in the third one (Table 2.). The pregnancy was complicated by gestational diabetes, however, it was sufficiently controlled with dietary measures alone. C-section was performed at 37th week of gestation. A healthy baby was born. Soon after the patient finished breastfeeding a routine MRI scan was performed. It showed residual tumour progression and SSA treatment was promptly reintroduced. (Fig. 3).

After 8 months of optimal disease control the patient became pregnant again and SSA therapy was withheld. Directly after withdrawal we did not observe any side effects related to lanreotide treatment. The second pregnancy was also complicated by gestational diabetes. In spite of the worse glycaemic control than in the previous pregnancy, the patient refused insulin treatment and followed dietary advice intervention only. In the second trimester she complained of persistent headaches, without visual impairment, and her biochemical control worsened (Table 2.). Therefore it was decided to initiate DA (cabergoline) that resulted in headache relief and a decrease in hormone concentrations (Table 2.). Treatment with SSA and MRI scan were considered in case dopamine agonist failed to alleviate the symptoms, but because clinical and biochemical improvement were reached, they were not deemed necessary. The patient underwent a C-section at 38th week of gestation delivering a large but otherwise healthy baby. Her body weight was 4350 g (>97th centile) and length was 56 cm (>97th centile). In this case the child's large birth weight might suggest macrosomy due to inadequate diabetes control during pregnancy. Four weeks after labour biochemical assessment showed elevated plasma IGF-1 concentration (IGF-1: 482 ng/ml, 1.7 x ULN) and MRI scan revealed further

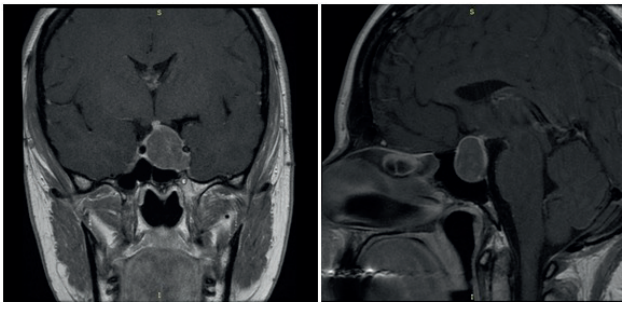

Figure 1. At diagnosis. Pituitary MRI T1-weighted, coronal section. Macroadenoma (19 x 25 x 24 mm) extending upwards into suprasellar region, comes into contact with the optic chiasm and invades left cavernous sinus.

Source: own study.

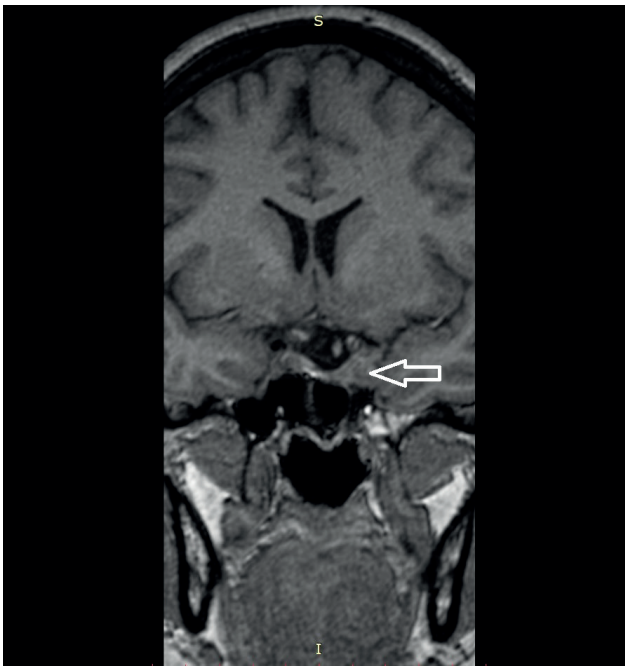

Figure 2. Post surgery. Visible tumour remnant in contact with left cavernous sinus, distorted optic chiasm.
Source: own study.

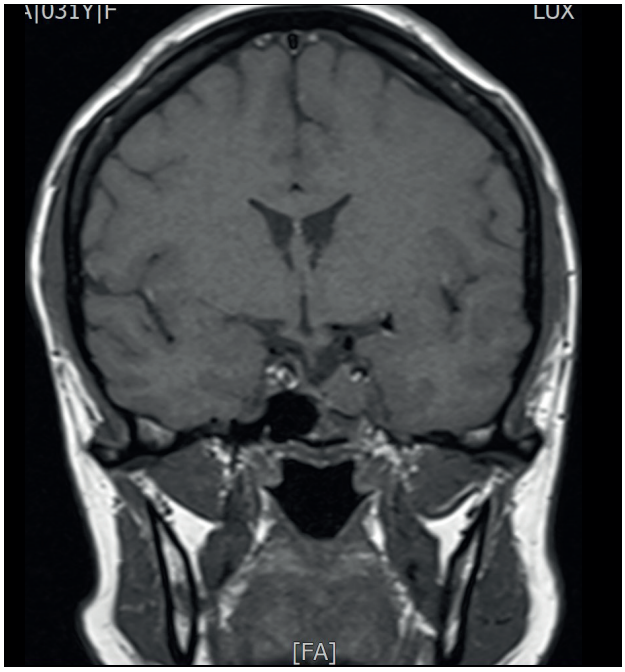

Figure 3. 9 months after first pregnancy. Tumour remnant (13 x 13 x 8 mm) invading left cavernous sinus and bulging into left sphenoidal sinus. The infundibulum and optic chiasm visibly distorted.
Source: own study.

progression of residual tumour. Because the patient was not breastfeeding, SSA has been instantly reinitiated leading again to optimal acromegaly control. At last follow-up both children had been developing normally.

Discussion

Pregnancy in acromegaly is a rare event as acromegaly is a rare disease with estimated prevalence of approximately 70 cases per million (1). It is typically diagnosed in forth to sixth decade of life so many female patients are not willing to get pregnant or they are postmenopausal. Additionally, young acromegalic women may frequently have impaired fertility due to gonadotropin deficiency caused by tumour mass effect (compression of the pituitary gland and its insufficiency) or hyperprolactinaemia (due to mixed tumours or pituitary stalk compression or deviation) (2). Treatment, such as surgical intervention or radiotherapy may also cause hypopituitarism. Although pregnancy in acromegalic patient is unusual, it is considered generally safe (3-8). It commonly occurs after successful surgical intervention or during pharmacological treatment, when satisfying disease control has been achieved (3, 7, 9, 10).

During physiological pregnancy placenta produces its own GH variant in increasing concentrations in the second half of pregnancy. Placental GH is not affected by GHRH but it exhibits a negative feedback on pituitary GH secretion

Table 2. Evolution of GH and IGF-1 levels.

	GH ug/l	IGF-1 (NR: 118-294 ng/ml)
Diagnosis	6.2	701
Lanreotide Autogel 120 mg 4 months	0.46	212
Post surgery	2.78	426
1st trimester of the 1st pregnancy	3.25	297
2nd trimester of the 1st pregnancy	2.38	353
3rd trimester of the 1st pregnancy	1.34	403
Lanreotide Autogel 120 mg 6 months	0.76	280
1st trimester of the 2nd pregnancy	0.83	160
2nd trimester of the 2nd pregnancy	4.09	520
3rd trimester of the 2nd pregnancy	1.79	444
Four weeks postpartum	2.84	482

Source: own study.

and becomes the major hormone stimulating the production of maternal IGF-1. Further, during the first trimester the increase in oestrogen concentration induces a state of GH resistance in the liver, which subsequently contributes to decreased IGF-1 levels. Nonetheless, increasing concentration of placental GH after mid-gestation usually overcomes this resistance and IGF-1 level begins to rise (4, 7, 9, 11-14).

In pregnant women with acromegaly oestrogen-induced hepatic GH resistance also occurs. Therefore, one may expect a biochemical and clinical improvement in the first trimester of pregnancy. However, it should be noted that in acromegaly GH secretion by the pituitary adenoma is largely autonomous. After mid-gestation both pituitary and placental GH variants coexist and they counteract the liver resistance. Therefore, biochemical control of acromegaly during pregnancy depends on the interplay between the pituitary GH, placental GH and oestrogen derived resistance, all of which are highly variable among individuals. Nevertheless, in many reported cases, acromegaly was well controlled, with stable IGF-1 concentrations throughout pregnancies, similar to preconception levels (3-7, 9). Conventional assays do not distinguish between the two GH forms (pituitary and placental). Thus, routine measurements of GH concentration in asymptomatic pregnant patients with acromegaly are not recommended (4, 15).

Pregnancy is considered to stimulate pituitary gland to increased its volume by nearly double its size with the highest values during first days postpartum. That occurs due to hypertrophy and hyperplasia of lactotrophs. However, pituitary height usually does not exceed 10 mm in the third trimester and in normal pregnancy signs and symptoms of pituitary enlargement do not appear (7, 16, 17). In women with pituitary tumours headaches or visual disturbances may reflect tumour growth, but also physiological pituitary gland enlargement in an already restricted intrasellar space (7, 18).

It is recommended to discontinue treatment with long-acting somatostatin analogues or pegvisomant two months before conception (15). However, in most patients pregnancy occurs during treatment with long-acting SSA and/or pegvisomant and/or dopamine agonists. In such situation the treatment should be discontinued and reintroduced only for tumour and headache control. In our patient, therapy with SSA was withdrawn as soon as the pregnancy was confirmed. Discontinuation of treatment potentially may cause tumour enlargement with clinical manifestation, such as visual impairment or severe headache. However in majority of cases no tumour growth was reported. Just as the course of acromegaly during pregnancy is stable in most patients, the same applies to MRI imaging results (3, 4, 7, 9, 10). The tumour volume usually does not increase, however, routine radiological examination is not common. Nevertheless, cases of asymptomatic tumour growth detected on MRI scans have rarely been reported (3, 19). If symptoms of tumour expansion occur, medical or surgical treatment should be implemented (15, 20). In our patient persistent headache developed during second pregnancy but MRI imaging was not necessary because of prompt symptoms alleviation upon start of cabergoline treatment and no visual field defect present. Patients treated during pregnancy should be closely monitored in case any adverse events occur. MRI imaging and hormonal tests are indicated when clinical complications appear and therapeutic decisions have to be made (7, 15, 21).

Acromegaly itself has no adverse effect on foetus development. Haliloglu et al. compared physical status and intelligence scores of children of acromegalic mothers with children of healthy mothers and children of women with prolactinoma. Their conclusions were that pregnancies in acromegaly were in general uneventful and health status and IQ scores of children of mothers with acromegaly do not differ from the general population (22).

However pregnant women with acromegaly have higher risk of developing gravid hypertension and gestational diabetes especially when there was no disease activity control before conception (3). Modestly higher risk of developing gestational diabetes mellitus in acromegalics is probably associated with high frequency of insulin resistance due to GH antagonism to insulin. Patients with acromegaly could already have prediabetes before pregnancy, as it was observed in our patient, and pregnancy itself poses an insulin-resistant-state (3, 5, 9). Subsequently, gravid hypertension and gestational diabetes increase the risk of delivering a baby with microsomia or macrosomia, respectively (7, 23). Despite discontinuation of pharmacological therapy in most cases pregnancy in acromegaly is uneventful and newborns are unaffected (3, 6, 9, 10). On the other hand, altered neonatal weight could be associated with medical treatment during pregnancy (7, 10).

Somatostatin analogues are known to cross the placental barrier, but in most cases of foetal exposure there were no adverse maternal of foetal outcomes (3, 8, 9, 10, 20, 24-27). Notwithstanding, cases of small-for-gestational-age infants were reported (3, 7, 10). A suspected mechanism is transient decreases of blood flow in uterine artery following drug injections (27). Dopamine agonists have also been shown to cross the placenta, but they have not been associated with altered birth weight, congenital malformations or increased risk of miscarriage or preterm deliveries (3, 6, 28-30). Most of aforementioned data was derived from studies regarding usage of dopamine agonists in patients with prolactinoma but they lessens concern for DA use in acromegaly as well (15). Although reports regarding pregnant women with acromegaly treated with pegvisomant are very scarce, there is no data that would suggest adverse consequences on pregnancy outcome (31). However, pegvisomant usage in pregnancy requires further studies and is not recommended unless absolutely necessary.

Presented patient has been treated with cabergoline, with rapid recovery from headache, improvement of GH and IGF-1 concentrations and no adverse effects.

Breast feeding during active acromegaly seems safe to newborns (6, 7), though data is insufficient. Somatostatin analogues are secreted into breast milk, but their effects on infants might be irrelevant due to negligible absorption (7, 27).

Conclusions

Pregnancy in a woman with acromegaly is generally safe, both from maternal and foetal perspective. In most cases pregnancies progress uneventfully, with stable tumour size and GH/IGF-1 concentrations. Thus routine hormonal measurements, pituitary MRI imaging and continuation of pharmacological treatment during pregnancy are not recommended. Rarely tumour expansion with clinical signs, such as visual field loss or headache, may occur. Then treatment options include both medical and surgical intervention. Somatostatin analogues, dopamine agonists and pegvisomant are considered safe if used during pregnancy but still not sufficient data are available. Complications of the pregnancy such as gravid hypertension and gestational diabetes tend to be more often in acromegalics, especially

if disease activity control before conception was no sufficient or acromegaly was diagnosed during pregnancy.

In premenopausal women with acromegaly choice of treatment should be guided by patient's individual procreative plans because certain therapeutic interventions such as surgery or radiotherapy may cause infertility or subfertility.

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