SPONTANEOUS CONCEPTION AND TERM DELIVERY IN A WOMAN WITH UNCONTROLLED ACROMEGALY AND HYPOGONADOTROPIC HYPOGONADISM

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Abstract

Background. Patients with acromegaly (caused by growth-hormone-secreting pituitary adenomas) are at increased risk of hypopituitarism, in particular hypogonadotropic hypogonadism, before and after multimodal therapy. In affected women of reproductive age, fertility is impaired and complex fertility treatments are needed to achieve conception.

Case presentation. We present the case of a young woman with acromegaly caused by a GH-secreting macroadenoma with suprasellar and bilateral cavernous sinus extension; hypogonadotropic hypogonadism and secondary hypothyroidism were present from the initial evaluation. Neurosurgical intervention was repeatedly recommended but the patient refused it initially; also she was non-compliant to the medical treatment of acromegaly. Transsphenoidal tumor debulking with adjuvant gamma-knife radiotherapy was eventually performed. Following treatment persistent active acromegaly and hypogonadotropic hypogonadism were diagnosed. Under chronic estroprogestative replacement therapy, the patient conceived and delivered a full-term healthy newborn without any complications. Possible mechanisms are discussed.

Conclusions. Secondary hypogonadotropic hypogonadism in pituitary patients, even when considered permanent (after surgery and radiotherapy), can exceptionally allow spontaneous conception and normal course of pregnancy.

Key words: hypogonadotropic hypogonadism, acromegaly, pregnancy, spontaneous conception.

BACKGROUND

Hypogonadism and infertility are frequent in untreated acromegaly (most frequently due to pituitary macroadenomas) (1), and they affect more than half of the women of reproductive age with acromegaly. The most frequent mechanism causing amenorrhea and infertility in acromegaly has decreased gonadotropin secretion. Low gonadotropin levels are caused either by the expanding

tumor mass or by the associated hyperprolactinemia, which is observed in 40% of patients with acromegaly (2, 3). When persistent despite adequate management of acromegaly, hypogonadotropic hypogonadism is associated with lower chances of obtaining a live birth even with the use of sophisticated assisted reproduction techniques (4).

CASE PRESENTATION

We present the case of a 22 years-old woman initially referred to the Pituitary and Neuroendocrine Department of the “C.I. Parhon” National Institute of Endocrinology in Bucharest in June 2010 for secondary amenorrhea unresponsive to progestatives, primary infertility, frequent headaches and marked acromegalic features, which had progressed for 3 years before diagnosis.

Clinical examination revealed a severe acromegalic phenotype, mild obesity (BMI 30.8 kg/sqm), thick, oily skin with multiple nevi, bilateral galactorrhea. No signs of hyperandrogenism were evident. Clinical signs of thyroid and adrenal failure were absent and no visual field defects were present.

The laboratory evaluation revealed markedly increased GH and IGF-1 secretion, mild hyperprolactinemia, as well as thyrotropin and gonadotropin deficiency (Table 1). The serum concentrations of androgens were normal.

A contrast-enhanced pituitary CT scan revealed a large pituitary macroadenoma, with suprasellar extension and invasion of both cavernous sinuses (Fig. 1). The genetic analysis revealed no pathogenetic AIP gene mutation.

Transsphenoidal surgery was recommended but the patient refused the intervention. Thyroxine replacement (initially 50, progressively increased to 100μg L-thyroxine daily) and treatment with

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Figure 1. Contrast-enhanced pituitary CT coronal sections during follow-up: A) June 2010, at diagnosis: large pituitary mass with suprasellar and infrasellar extension (sphenoid sinus), invasive to both cavernous sinuses (arrow) B) Feb 2014, after surgery and 11 months after gamma-knife radiotherapy: a small tumor remnant with bilateral cavernous sinus invasion is observed (arrow).

somatostatin analogues (SSA) - lanreotide 30 mg every 14 days were initiated. Despite good clinical tolerance, the patient discontinued SSA administration after 3 months and responsiveness to treatment could not be assessed. During follow-up, the patient consistently refused surgery or further administration of SSAs; consequently, clinical and biochemical worsening of her acromegaly occurred (Table 1). On the other hand, the patient was compliant to the replacement therapy with thyroxine and estroprogestatives (estradiol and norgestrel- Cycloprogyova).

Two years and 5 months after the diagnosis, the patient consented to transsphenoidal surgery, which resulted in significant tumor debulking, with a relatively large postoperative remnant. GH and IGF-I levels decreased but were still abnormal, while prolactin levels normalized (Table 1). The immunohistochemical evaluation was not available but the modest preoperative hyperprolactinemia and

the complete normalization of prolactin after tumor debulking suggested initial stalk effect. Gamma-knife radio-surgery was performed three months later.

Soon after radio-surgery, the patient expressed her desire to become pregnant; therefore gonadotroph and ovarian function were re-assessed after temporary discontinuation of the gonadal replacement therapy for 3 months. During treatment discontinuation the patient was again amenorrhoeic and persistent hypogonadotropic hypogonadism, despite the correction of hyperprolactinemia was demonstrated (Table 1). We resumed the gonadal replacement therapy and scheduled the next follow-up visit. The patient did not attend the scheduled visit and only presented after more than 1 year (in April 2015) complaining of weight gain and amenorrhea despite correct administration of cyclical estroprogestative replacement. Clinical and ultrasonographical examination revealed a normal third trimester pregnancy. Blood pressure and visual fields were normal, and there was no gestational diabetes mellitus. One month later the patient delivered uneventfully a healthy baby boy, of normal size and weight, via vaginal route. Replacement therapy was continued until birth and thereafter. The patient is currently breastfeeding. A single IGF-1 measurement performed 3 months after delivery revealed an increased concentration: 761.5 ng/mL.

DISCUSSION

We present the unusual case of a young woman with inadequately controlled acromegaly after pituitary tumor debulking and adjuvant pituitary radiotherapy persisting, who conceived spontaneously and carried the pregnancy uneventfully through to term despite

Table 1. Hormonal parameters of pituitary function in our case, at presentation, after therapy and during pregnancy

	Nadir GH in OGTT (ng/mL)	IGF-1 (ng/mL)	Cortisol after Synacthen (µg/dL)	FSH (mIU/mL)	LH (mIU/mL)	Estradiol (pg/mL)	PRL (ng/mL)	TSH (µU/mL)	Free T4 (pmol/L)
Normal range	<1	116-358	>20	3.8-8.7*	2.2-10.9*	27-122*	3-29	0.5-4.5	12-22
Time									
Jun 2010	141	1487	24.41	1.7	2.74	17.7	37.35	0.9	9.9
Dec 2011	187.6	978.4	24.3	2.8	1.19	36.04	33.81	1.7	8.4
Dec 2012 transsphenoidal surgery									
Feb 2013	40.4	969.1	-	Not done (on gonadal replacement)			11.2	1.19	14.04
March 2013 gamma-knife radiosurgery									
Nov 2013	45.2	N/A	30.7	Not done (on gonadal replacement)			-	0.87	12.57
Feb 2014									
(discontinued EPreplacement 3 months)	15.3	942.9	-	4.6	3.6	15	24	0.41	13.2
Apr 2015	15.6	382.7	Basal 14.3	0.82	0.29	>5000		0.8	12.3

*normal range for follicular phase. EP-estroprogestative

confirmed hypogonadotropic hypogonadism.

Normal pregnancy and childbirth in patients with hypogonadotropic hypogonadism is not frequent even when using modern assisted reproduction techniques (5-7). Complex fertility treatments have been used in all the reported cases and proved efficient in achieving ovulation (in almost all cases, in around 60% of treatment cycles) (4). However, even when conception is achieved, the course of pregnancy is at significantly higher risk compared to healthy women: there is an increased risk of miscarriage, which affects more than one third of cases) (4), a relatively small (11%) but significant risk of intrauterine death in mid-pregnancy and increased risk of complex uterine dysfunction leading to small-for-gestational-age newborns, transverse presentations and postpartum hemorrhage (4; 8-10). Overall, slightly less than one half of hypogonadotropic hypogonadic women with acromegaly being offered assisted reproduction achieve a live birth (4).

Reports of spontaneous conception in hypogonadotropic hypogonadism are rare. The phenomenon is not so uncommon in patients with idiopathic hypogonadotropic hypogonadism (IHH), in whom reversal of hypogonadism can be observed in up to 22% of cases, across a wide range of genotypes (11). However, in acquired hypogonadotropic hypogonadism (e.g. Sheehan's syndrome), the reversal of decreased gonadotropic function and natural conception is an exceptional occurrence (12). To our knowledge, no such case in pituitary adenoma patients with confirmed hypogonadism after surgery and radiotherapy has been previously reported.

The possibility of reversal of hypopituitarism prior to conception is, in our opinion, unlikely in our case. Hypogonadotropic hypogonadism has been confirmed from the diagnosis of acromegaly and reconfirmed after surgery (which could induce reversal of hypopituitarism in as much as half of cases) (13). In addition, gammaknife radiotherapy increases the risk of permanent hypopituitarism (14).

Therefore we conclude that our patient spontaneously conceived despite persistent acquired hypogonadotropic hypogonadism. A number of possible mechanisms can be offered, but all are speculative due to the rarity of the phenomenon. Occasional release of gonadotropins from the residual pituitary tissue, in sufficient amounts to induce sporadic ovulation, although plausible, is yet to be demonstrated. The estradiol administered as part of the gonadal replacement therapy offered to our patient could have a beneficial effect on the follicular growth (15). Also, fluctuations

in the drug administration (possible in a generally non-compliant patient) could theoretically trigger ovulation but this has never been proved in a patient with chronic hypogonadotropic hypogonadism.

In addition, excessive serum GH levels can exert mixed effects on the ovarian function with both direct (16) and indirect (hyperinsulinism-mediated) (17, 18) stimulatory effects on the ovarian androgen production. These seemingly deleterious effects can be counterbalanced by an autocrine effect of the GH-induced ovarian IGF secretion (particularly IGF II), which would augment the ovarian response to gonadotropins (19). In fact, exogenous GH is sometimes administered to women who respond poorly to controlled ovarian hyperstimulation during assisted reproductive techniques (20). The net result of the interplay between these complex mechanisms of GH / IGF action in the ovaries of women with acromegaly has not been studied to date. In a large series of acromegalic women, a minority of the patients desiring pregnancy achieved it, but only after GH/IGF I normalization (21).

Reversal of hypogonadism as a consequence of progressive remission of acromegaly in the year before pregnancy cannot theoretically be overruled (the GH/IGF-1 values measured in the third trimester of pregnancy were significantly lower compared to previous values - see Table 1). However, after delivery, a single measurement of IGF-1 was markedly increased, arguing against significant disease remission. Unfortunately the patient did not return to clinic for a full endocrine re-evaluation.

Another remarkable feature in the evolution of our patient was the normal course of pregnancy and birth despite uncontrolled acromegaly. Pregnancy in women with acromegaly raises a number of clinical problems. The major concern is the potential tumor expansion, attributed to the growth-promoting effect of estrogens, and the consequent risk of visual field defects and neurological complications (18). The medical treatments in use for acromegaly (SSA, GH receptor antagonist) are not approved during pregnancy (22, 23); only dopamine agonists can be used if necessary, although their efficacy is limited (disease control is only achieved in 10% of cases) (24). In practice, medical treatment can be safely withdrawn after conception in most cases (22). Our patient received no medical treatment and complained of no symptoms suggestive of complications during pregnancy. The radio-surgery might have contributed to this, by limiting the potential for tumor growth. Uncontrolled acromegaly also can aggravate the increased insulin resistance of normal pregnancy, leading to a theoretically

increased risk of hyperglycemia and hypertension, which pose potential risks to the mother and fetus. Despite these considerations, in a review of pregnancies of women with a wide spectrum of clinical scenarios of acromegaly, it has been concluded that acromegaly itself rarely affects the clinical course of pregnancy (25). None of these complications were present in our patient at the time of the evaluation, late in her pregnancy (unfortunately, the patient's compliance to scheduled medical visits has been very low throughout follow-up and this explains the very late presentation during pregnancy).

Despite the severe clinical, biochemical and imaging picture, our patient did not harbor an AIP mutation (AIP - related pituitary adenomas, frequently somatotroph, either familial or sporadic are usually diagnosed in younger patients and are larger and more invasive) (26).

In conclusion, the exceptional possibility of spontaneous conception in pituitary adenoma patients of reproductive age with confirmed hypogonadotropic hypogonadism should be acknowledged. This can lead to an improvement of the clinical management of these cases as well as of our understanding of the pathophysiology of pituitary function after complex therapy of pituitary adenomas.

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Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004; 101(3):613-619.
2. Katznelson L, Kleinberg D, Vance ML, Stavrou S, Pulaski KJ, Schoenfeld DA, Hayden DL, Wright ME, Woodburn CJ, Klibanski A. Hypogonadism in patients with acromegaly: data from the multi-centre acromegaly registry pilot study. *Clin Endocrinol (Oxf)* 2001; 54(2):183-188.
3. Grynberg M, Salenave S, Young J, Chanson P. Female gonadal function before and after treatment of acromegaly. *J Clin Endocrinol Metab* 2010; 95(10):4518-4525.
4. Hall R, Manski-Nankervis J, Goni N, Davies MC, Conway GS. Fertility outcomes in women with hypopituitarism. *Clin Endocrinol (Oxf)* 2006; 65(1):71-74.
5. Golan A, Abramov L, Yedwab G, David MP. Pregnancy in panhypopituitarism. *Gynecol Obstet Invest* 1990; 29(3):232-234.
6. Lindsay JR, Nieman LK. The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. *Endocr Rev* 2005; 26(6):775-799.
7. Pilka L, Snajderova M, Rumpik D, Kaplanova T, Pilka R. [Pregnancy and delivery after traumatic panhypopituitarism]. *Ceska Gynecol* 2003; 68(4):277-279.
8. Kubler K, Klingmuller D, Gembruch U, Merz WM. High-risk pregnancy management in women with hypopituitarism. *J Perinatol* 2009; 29(2):89-95.
9. Overton CE, Davis CJ, West C, Davies MC, Conway GS. High risk pregnancies in hypopituitary women. *Hum Reprod* 2002; 17(6):1464-1467.
10. Shoham Z, Balen A, Patel A, Jacobs HS. Results of ovulation induction using human menopausal gonadotropin or purified follicle-stimulating hormone in hypogonadotropic hypogonadism patients. *Fertil Steril* 1991; 56(6):1048-1053.
11. Sidhoum VF, Chan YM, Lippincott MF, Balasubramanian R, Quinton R, Plummer L, Dwyer A, Pitteloud N, Hayes FJ, Hall JE, Martin KA, Boepple PA, Seminara SB. Reversal and relapse of hypogonadotropic hypogonadism: resilience and fragility of the reproductive neuroendocrine system. *J Clin Endocrinol Metab* 2014; 99(3):861-870.
12. Algun E, Ayakta H, Harman M, Topal C, Aksoy H. Spontaneous pregnancy in a patient with Sheehan's syndrome. *Eur J Obstet Gynecol Reprod Biol* 2003; 110(2):242-244.
13. Nomikos P, Buchfelder M, Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. *Eur J Endocrinol* 2005; 152(3):379-387.
14. Pollock BE. Radio-surgery for pituitary adenomas. *Prog Neurol Surg* 2007; 20:164-171.
15. Britt KL, Findlay JK. Estrogen actions in the ovary revisited. *J Endocrinol* 2002; 175(2):269-276.
16. Nestler JE. Stimulation of androgen production by insulin-like growth factor I. *Ann Intern Med* 1986; 105(5):796.
17. Kaltsas GA, Androulakis II, Tziveriotis K, Papadogias D, Tsikini A, Makras P, Dimitriou K, Stathopoulou A, Piaditis G. Polycystic ovaries and the polycystic ovary syndrome phenotype in women with active acromegaly. *Clin Endocrinol (Oxf)* 2007; 67(6):917-922.
18. Herman-Bonert V, Seliverstov M, Melmed S. Pregnancy in acromegaly: successful therapeutic outcome. *J Clin Endocrinol Metab* 1998; 83(3):727-731.
19. Barreca A, Artini PG, Del Monte P, Ponzani P, Pasquini P, Cariola G, Volpe A, Genazzani AR, Giordano G, Minuto F. *In vivo* and *in vitro* effect of growth hormone on estradiol secretion by human granulosa cells. *J Clin Endocrinol Metab* 1993; 77(1):61-67.
20. Surrey ES, Schoolcraft WB. Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. *Fertil Steril* 2000; 73(4):667-676.
21. Grasso LFS, Galdiero M, Auriemma RS, Cozzolino A, Vitale P, Simeoli C, Pivonello R, Colao A. Fertility rate in acromegalic women: a single center experience on 70 patients before and after treatment. *Endocrine Abstracts* (2011); 26 P257.
22. Caron P. Acromegaly and pregnancy. *Ann Endocrinol (Paris)* 2011; 72(4):282-286.
23. Ben Salem Hachmi L, Kammoun I, Bouzid C, Smida H, Nagi S, Turki Z, Ben Slama C. [Management of acromegaly in pregnant woman]. *Ann Endocrinol (Paris)* 2010; 71(1):60-63.
24. Newman CB. Medical therapy for acromegaly. *Endocrinol Metab Clin North Am* 1999; 28(1):171-190.
25. Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F. Pregnancy and pituitary disorders. *Eur J Endocrinol* 2010; 162(3):453-475.
26. Baci I, Radian S, Capatina C, Botusan I, Afloriei D, Stancu C, Dumitrascu A, Ciubotaru V, Coculescu M. The p.R16H (C.47G>A) AIP gene variant in a case with invasive non-functioning pituitary macroadenoma and Screening of a Control Cohort. *Acta Endocrinol (Buc)* 2013; IX(1): 97-108.