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CASE REPORT

Safe treatment with somatostatin analogues in a woman with acromegaly whilst pregnant and lactating

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Abstract

CONTEXT: Pregnancy in acromegaly is rare, there have been few case reports and series published to date. Also breastfeeding under acromegaly treatment is extremely rare. The late diagnosis of pregnancy in acromegaly will sometimes dictate the treatment and management of the patient.

MATERIAL AND METHOD: We present a 32-year-old woman with acromegaly, a late diagnosed pregnancy and a completed fetal organogenesis. Due to the gestation time and bothersome headaches accompanying a pituitary macroadenoma, we decided to continue long lasting somatostatin analogues treatment but with increased injection intervals of 6 weeks. We also continued this treatment during 12 months of breastfeeding.

RESULTS: Our treatment did not cause any complication of premature birth or any health problems with the newborn baby. The child has since developed normally up to the age of 5.

CONCLUSION: The course of acromegaly disease and the time of pregnancy diagnosis may prompt suitable drug and treatment regimes. We administered effective and safe somatostatin analogues treatment during gestation and breastfeeding which was safe for both mother and baby.

Abbreviations:
GH - growth hormone
IGF - insulin growth factor
MRI - magnetic resonance

INTRODUCTION

Acromegaly is characterized by the increased secretion of growth hormone (GH). The cause in more than 99% of cases is a GH secreting pituitary tumor (Petersenn *et al.*. 2019). As acromegaly is linked to the high incidence of secondary hypogonadism, pregnancies in such patients are relatively rare. However, some women with acromegaly do get pregnant and this situation raises a lot of questions regarding complications and treatment.

It is strongly advised to stop any medical intervention during pregnancy, but a case-by-case approach is recommended (Katznelson *et al.* 2014; Chanson *et al.* 2019).

To date only a few case reports and series of acromegaly in pregnant patients have been published (Hannon *et al.* 2019; Dias *et al.* 2013; van der Lely *et al.* 2015).

We present our experience with a pregnant woman with acromegaly disease whose pregnancy was confirmed late and led to our decision to continue to treat her with somatostatin analogues therapy.

CASE PRESENTATION

A 32-year-old woman was admitted to the Department of Endocrinology Medical University of Gdansk with suspected acromegaly. She had suffered headaches for over 3 years with sweating, and enlarged hands and feet. In addition, she appeared to have signs of prognathism, had irregular periods and a problem conceiving children.

No family history of pituitary disease was reported.

INVESTIGATION

Her plasma GH concentration was significantly elevated at 43,8 ng/mL, and following a glucose load: 57 ng/ml; 45,6 ng/ml; 59,20 ng/ml. Her plasma glucose concentration was slightly elevated at 105 mg/dL (reference value 60 – 99 mg/dL), her plasma IGF – 1 concentration was elevated at 878,8 ng/mL (reference value 85 – 283 ng/mL), her prolactin was 922 mU/L (reference value in non-pregnant female 127 – 637 mU/L). Her baseline blood results are summarized in Table 1.

After diagnosing acromegaly, we decided to perform an MRI examination. The MRI of her pituitary gland with a gadoline contrast confirmed a 1,9 x 1,8 x 1,3 cm mass with distortion of the infundibulum, without impression on the optic chiasma (Figure 1).

We started therapy with somatostatin analogues every 4 weeks and the patient showed good tolerance. Her menstruation was irregular throughout (every 2 – 3 months). As the patient complained increasingly of headaches, we decided after 5 months to perform another MRI imaging of the pituitary gland. The pituitary tumor was found to be stable in size so we continued somatostatin analogues therapy at 4-week intervals.

After 6 months of somatostatin analogues therapy, the patient started to complain of abdominal pain, flatulence and constipation. Taking account of these symptoms, we examined the patient by abdominal ultrasound and the test results showed the presence of a living fetus in her uterus with completed organogenesis. She continued to suffer from headaches, and sweating.

The consultant gynecologist estimated her pregnancy at 28 weeks and on examination found no complication with fetal development. The mother had neither hypertension or gestational diabetes. We made the decision to continue somatostatin analogues therapy, but we widened the injection intervals to every 6 weeks. The headaches intensified seven days before the patient was due her next dose of analogues. The control visual field examination was normal.

She carried the baby to full term and gave birth at 39 weeks of pregnancy by caesarean section. The fetal weight was 3,4 kg at birth with an APGAR score of 10. The neonate was examined by an experienced neonatologist and no congenital abnormalities were identified. Our patient was determined to breastfeed her newborn baby, so we decided to continue somatostatin analogues every 6 weeks. Six months after delivery the patient's menstruation has returned to normal with a regular cycle every 33 days. The patient's headaches got worse, as did the sweating and feeling of swelling in the hands and feet.

A repeat contrast MRI showed stable pituitary tumor 1,9 x 1,8 x 1,3 cm with slight compression of the infundibulum, but without detriment to the optic chiasma. Due to the patient's malaise and the increase in the parameters of diseases IGF 1 1009 nmol/L, we decided to increase the frequency of the somatostatin analogues administration to every 4 weeks. We continued treatment with these analogues and referred her for surgery. Fifteen months after delivery she underwent transsphenoidal surgery of the pituitary tumor. Immunohistochemical analysis of her adenoma stained positively for GH but did not stain for PRL, FSH, LH, TSH or ACTH.

Three months after surgery hormonal analysis showed persistent GH hypersecretion and monthly somatostatin analogues were restarted. Due to tumor residual mass we decided to refer the patient for radiotherapy as the surgeon said an operation on the tumor was too risky. As of the latest update her daughter has developed perfectly normally at the age of 5.

DISCUSSION

Acromegaly is a rare disorder brought about by a pituitary gland tumor producing excess GH. Fertility in acromegaly is impaired as a result of both hypogonadism and the treatment for acromegaly itself (Grynberg *et al.* 2010; Muhammad *et al.* 2017). Therefore, pregnancy is extremely rare with about 200 cases reported in literature. During pregnancy the severity of the disorder has been shown to improve (Shimatsu *et al.* 2010; Lau *et al.* 2008), remain stable or worsen (Dias *et al.* 2013; Cheng at at 2012).

Optimal management of acromegaly during pregnancy has not been established. An update on clinical care for pregnant women with acromegaly implies treatment discontinuation before or at confirmation of pregnancy (Chanson *et al.* 2019). Pharmacological treatment with somatostatin analogues has been

Tab. 1. Baseline endocrine laboratory evaluations

	Results before pregnancy/ treatment	Results at pregnancy 28/40	Results 10 month post-partum	Normal range
Free T4 (pmol/L)	14,3	12,9	16,5	10 - 25
TSH (mIU/L)	2,23	0,98	1,2	0,35-4,94
IGF1 (ng/mL)	878,8	632,50	1009,0	85 - 283
GH (ng/mL)	43,8	Not done	6,21	-
Prolactin (mU/L)	922	882,02	Not done	127 - 637
Morning serum Cortisol (nmol/L)	288,8	197,9	175	101-536
Morning plasma ACTH pg/mL	42,4	Not done	36,9	15 -46
FSH (IU/L)	9,11	Not done	No done	3,03-8,08
LH (mIU/mL)	4,62	Not done	1,69	1,4 -9,6
Estradiol (pmol/L)	256	4715	Not done	77,1-921,2

associated with the decreased length in newborn children (Maffei *et al.* 2010). Although discontinuation of medical treatment during pregnancy has normally been advised, medical treatment with somatostatin analogues may be attempted before resorting to surgery.

During pregnancy there were no clear symptoms of disease activity re-emerging after the treatment was stopped. A persistent headache with or without visual disturbances is a common complaint in pregnant women with acromegaly (Hannon *et al.* 2019). This symptom could not be attributed to tumor enlargement or IGF 1 level which remained stable during gestation. The majority of patients with headaches during pregnancy also suffered headaches prior to the acromegaly treatment commencing (Dias *et al.* 2013; Abucham *et al.* 2017). On the other hand, the somatostatin analogs have an analgesic effect which is not associated with GH or IGF 1 suppression but could be an effect of inhibition of an unknown pro-nociceptive peptide (Levy *et al.* 2003; Matharu *et al.* 2004). We believe that the use of somatostatin analogues treatment probably relieved our patient's headaches.

The prevalence of diabetes mellitus and hypertension in acromegaly patients would be expected to increase markedly in acromegaly due to the known effects of excess GH and pregnancy on insulin resistance (Dias *et al.* 2013; Caron *et al.* 2010). We did not however observe these problems in our patient.

The approach for the treatment of acromegaly during gestation, taking into account the risk and benefit of treatment against not treating for both mother and fetus. Some pregnant women with acromegaly may have developed diabetes mellitus, glucose intolerance, or hypertension. Their newborns therefore have a higher risk of macrosomia or microsomia respectively (Dias *et al.* 2013; Kintiraki *et al.* 2015).

Although somatostatin analogues cross the placenta barrier and the placenta has somatostatin receptors, no serious adverse fetal effects were detected (Dias *et al.* 2015; Shimatsu *et al.* 2010; Caron *et al.* 2010; Assal *et al.* 2016; de Menis *et al.* 1999; Takano *et al.* 2006. The main side effect of somatostatin analogues treatment is low birth weight probably due to decreased blood flow in the uterine artery which was detected after the somatostatin analogues injection (Maffei *et al.* 2010).

Documented evidence of fetal complications due to exposure to long lasting somatostatin analogues are rare and even less known than with the complications due to the use of octreotide (Abucham *et al.* 2017; Caron *et al.* 2010; de Menis *et al.* 1999). Somatostatin analogues are not routinely administered to pregnant patients with acromegaly but for each patient the risks and benefits should be carefully weighed up before any decision on therapy is made.

There are several reports concerning the safe use of octreotide LAR in women with active acromegaly during pregnancy. In these case reports the women successfully delivered healthy children and no adverse effects on the fetus were detected in these cases (Neal, 2000; Brian *et al.* 2007).

Due to the gestation time required to complete organogenesis combined with bothersome headaches being suffered by our patient (as a result of the pituitary macroadenoma), we decided to continue long lasting somatostatin analogues treatment but with increased intervals of 6 weeks in-between injections. Our treatment did not cause any premature birth or health complications with the newborn baby. The child has since developed normally at age 5.

Transient and total exposure to pegvisomant during pregnancy has also been reported in a compilation of Pfizer's Global Safety Database (van der Lely *et al.* 2015). Twenty – seven cases were observed, most patients stopped pegvisomant when pregnancy was confirmed but three maintained it throughout pregnancy. The pegvisomant accumulates in very low concentrations in umbilical cord blood in spite of its therapeutic levels in maternal blood. Although no fetal

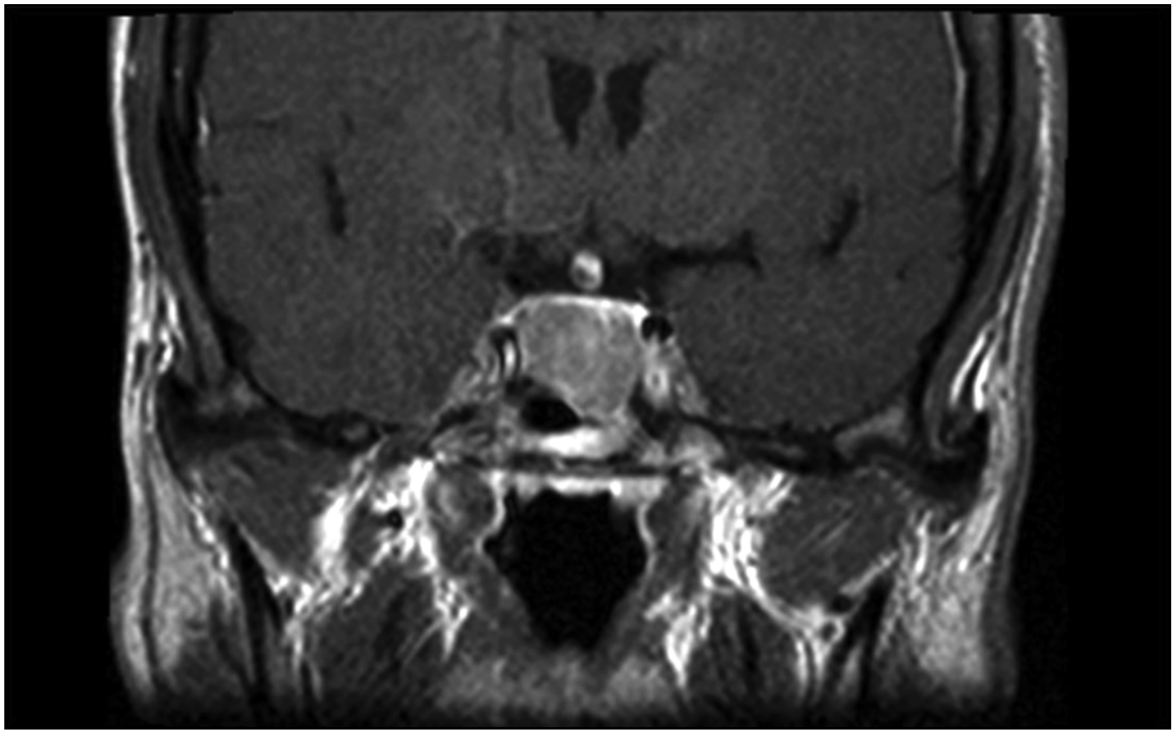

Fig. 1. MRI of pituitary gland with gadoline contrast confirmed a 1,9 x 1,8 x 1, 3 cm macoadenoma.

abnormalities were reported it should be noted that a higher rate of premature birth was attributed to exposure to pegvisomant (van der Laly *et al.* 2015).

Breastfeeding appears to be safe during active acromegaly for both mother and baby. There are no indications that breastfeeding promotes tumor growth (Dias *et al.* 2013). However, breastfeeding during acromegaly somatostatin analogues treatment is still controversial. Somatostatin analogues are excreted in breast milk but their biological activity and gastrointestinal absorption are unlikely to be of concern as they are ingested orally by the infant (Maffei *et al.* 2010). The cases presented involving children having been breastfed by women on somatostatin analogues treatment are extremely rare (Maffei *et al.* 2010). Our acromegaly patient continued breastfeeding for 12 months without any complications. We believe that the continuation of somatostatin analogues therapy helped to stabilized the pituitary tumor and her headaches.

CONCLUSION

Pregnancy in acromegaly is generally safe. We completely agree with the recommendation to discontinue somatostatin analogues treatment in pregnant women with acromegaly (Petersenn *et al.* 2019; Chanson *et al.* 2019). The course of acromegaly disease and the time of pregnancy diagnosis may prompt suitable drug and treatment regimes. We administered effective and safe somatostatin analogues treatment during gestation and breastfeeding which was safe for both mother and baby.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author's contribution statement

AB contributed to planning and conducting research, AB and HO provided direct care for the patient. KS approved the final draft submitted.

Ethics approval

Not applicable.

Consent for publication

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images. A copy of the written consent is available for review by the editorial board of this journal.

Competing interests

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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