Author's response to reviews

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Uneventful Octreotide LAR Therapy throughout Three Pregnancies, with Favorable Delivery and Newborn's Anthropometric Measures: a case report.

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Abstract

Introduction:
The safety of octreotide use - in its short acting preparation - in pregnancy is still unclear. This is the first documentation of uneventful octreotide LAR use, during three pregnancies in a young female suffering from bronchial carcinoid-associated ACTH-dependent Cushing’s syndrome.

Case presentation:
A 25 yr old Arab Muslim woman, presented to the emergency department suffering from rapid onset of headache, flaring acne and hirsutism, facial puffiness, weight gain and paroxysmal myopathy, and paranoiac thoughts of rape and sexual intimidation.

After surgical removal, the residual lung disease failed medical therapy. Chronic octreotide LAR injections were initiated, as indicated by positive Octreoscan. Follow-up revealed long-lasting positive response to octreotide. Avidity of Octreotide to Somatostatin receptor sub-type 2 (SSTR2) was later confirmed by positive SSTR-2 in the resected tumor specimen.

Despite instructions otherwise, the patient had three spontaneous pregnancies. During octreotide LAR therapy, she delivered three full-term healthy children.

Conclusion:
This case adds more data as to the potentially safe use of Octreotide, and the potential feasibility of Octreotide LAR use during pregnancy, making the patient's preference not to withdraw Octreotide as soon as pregnancy is confirmed, a thoughtful option.
**Introduction**

The safety of octreotide use during pregnancy does not lend itself to a controlled prospective study. Hence, such assessment is presently dependent on case reports.

Ectopic ACTH-dependent Cushing’s syndrome, associated with bronchial carcinoid is well-recognized. Though infrequent, it is the leading etiology (30%) of ectopic, non-pituitary, ACTH Secretion (EAS) (1). Currently, prognosis of bronchial carcinoid EAS is good (1-4), even when it persists or manifests as multiple lesions (5). This contrasts with the poor prognosis attributed this disease in the past (6).

When feasible, surgical removal of the causative tumor is the mainstay of treatment. Medical treatment can bridge the gap until surgical remedy, or provide adjunctive long-term therapy to suppress hormonal excess of residual disease.

Medical treatments include blockers of steroid synthesis (7) and Somatostatin analogues. (8) Once pregnancy is diagnosed, Somatostatin analogues were routinely discontinued, in much case reports during the last decade. Of special interest there were seven pregnant women; five with pituitary acromegaly (9-13), one with nesidioblastosis (14), and one with TSH producing pituitary macroadenoma (15) who delivered uneventfully concomitant to octreotide therapy throughout all trimesters. Five of these cases were treated with the short-acting preparation of Octreotide, while in two cases Octreotide LAR was the given preparation (12, 15). Until recently, only one case reported a short period (one month) use of long-acting Somatostatin-analogue preparation - Lanreotide, before it was discontinued at time of pregnancy confirmation (16).

We present the first case report study of a patient, who delivered three healthy babies following three consecutive pregnancies, while treated with octreotide LAR due to residual ectopic EAS.
Case presentation

In October 1999, a 25-year-old woman presented to the emergency department of our medical facility suffering from rapid onset of headache, flaring acne and hirsutism, facial puffiness, weight gain and paroxysmal myopathy, and paranoiac thoughts of rape and sexual intimidation.

Her physical examination revealed pronounced facial acne and hirsutism, oily skin, moon face, buffalo hump, and classical Cushing purplish skin striae in the abdominal, axillaries, and flanks regions. Blood pressure was 150/90 mmHg.

Table 1 presents the relevant endocrine profile. High-dose (2mg qid/day) dexamethasone failed to suppress both serum cortisol and urinary free cortisol (UFC) levels. Serum testosterone, DHEA-S, and 17-OH progesterone were within normal limits. Chest-computed tomography demonstrated a 22*15*10 mm mass in the upper segment of the left lower pulmonary lobe. No adrenal mass was detected.

The patient underwent a left lower lung lobectomy. Histopathology showed a typical carcinoid tumor without mitotic figures or necrosis, and with positive immunohistochemical stains for synaptophysin, neuron-specific enolase (NSE), chromogranin A, and strongly for ACTH.

The patient became completely free of symptoms with abnormal, though decreasing, UFC levels. A year and a half after surgery, she regained weight. Her physical examination confirmed moon face and re-darkening of previous striae. Her UFC levels were high, unsuppressed by either low or high doses of dexamethasone (table 1).

Computed tomography of the chest and abdomen were normal, as was subsequent pituitary tomography. An indium-111-pentetreotide scan to locate an occult focus of carcinoid revealed a hot focus in the left lower pulmonary lobe and upper right mediastinum. Steroid-synthesis blockers were initiated.

Mediastinal and para-tracheal histopathology of lymph node material obtained with thoracoscopy, showed a metastatic carcinoid. Following treatment with Sandostatin LAR (Octreotide 30 mg/month Novartis, Switzerland), she became symptom-free. Her endocrine laboratory results normalized (table 1).

Almost three years after surgery, while on Sandostatin LAR treatment, the patient became pregnant. She refused our recommendation to discontinue Sandostatin LAR therapy during the first trimester, as is routine (17). Rather, she insisted on continuing Sandostatin LAR, for the duration of the pregnancy due to its effectiveness in disease remission. A healthy full-term baby was born. Two and three years later
our patient delivered two more, healthy full-term babies. All deliveries were Cesarean sections.

Octreotide LAR treatment was continued throughout this time period.

Recent routine follow-up tomography of the chest (early 2009), revealed normal mediastinal lymph nodes, with permanent post-surgical changes at left lung basal portion. Concomitant test for urine 5-Hydroxy-indole-acetic acid (6.9 mg/24 hrs) was within normal limits (1-7 mg/24 hrs).

Immunohistochemistry assay to determine Somatostatin-receptor (SSTR) subtypes in tissue of the original carcinoid in the lung lobe was performed as previously described (18). The carcinoid tumor tested positive for SSTR -2A and SSTR-2B, and negative for SSTR – 1, 3, 4 & 5. The sample from the lymph node metastases was inadequate for SSTR immunohistochemistry.

Our patient’s three babies showed normal growth during up-to-128 months follow-up period (Figure 1).

Discussion

Octreotide in its short acting preparation has been used safely in humans since 1998. However, its safety during pregnancy is still uncertain. Its administration is usually stopped once pregnancy is confirmed, (17). Information regarding its safety during pregnancy is sparse. We document safe use of octreotide LAR (long acting compound) during one woman’s three consecutive full-term pregnancies, all uneventful and yielding healthy babies.

Octreoscan scintigraphy helps select carcinoid patients for Somatostatin analogue treatment (19).

Positive octreoscan indicates binding of the analogue for investigation (111In-DTPA-D-Phe¹-Octreotide) to SSTR subtypes 2, 3 and 5 (23). However, 18% of patients with positive octreoscan do not respond to Somatostatin analogue (23). Noteworthy, cases with good biochemical response or disease stabilization with octreotide treatment were positive for SSTR-2 staining. Those non-responsive were negative for SSTR-2 staining (22). It seems that response is virtue of octreotide binding to Somatostatin-Receptor subtype -2 (23). Though not essential for therapeutic decision-making, SSTR sub typing may elucidate our understanding of this rare and heterogeneous disease.

Octreotide crosses the placenta, where it remains stable (12, 13, 15, 20, 24). Respective maternal and infant serum Octreotide concentrations have been measured at 1009 vs. 353 (12), 4638-3676 vs. 3483 (13), 890 vs. 251 (20), and a range of 2888-5021 maternal vs. 101 pg/ml umbilical (15). Moreover, half-life elimination time of octreotide approaches 350 minutes in the infant (20), compared to 90 to 110 in
adults (25). Fetal exposure to octreotide, due to placental transfer and increased half-life in fetal serum has raised concern about its potential hazard to the fetus, (9).

Fetuses seem protected from the octreotide effect. Of primary concern are fetal growth and growth hormone levels during fetal life. During the third trimester, increasing placental growth hormone (GH) production leads to a significant rise in IGF-1 levels. In this regard, physiological changes of placental GH and IGF-1 were observed under Octreotide throughout pregnancy (14). Similar changes had been reported during Octreotide administration in the last part of pregnancy in a TSH-producing pituitary adenoma patient (15).

Octreotide-driven suppression of GH, however, is tampered since placental SSTRs are mainly of subtype-4, while SSTR-1 remains nonfunctional due to its low affinity to octreotide (26). Another report found a scanty binding of somatostatin and its analogues to both placental and umbilical cord diverse SSTR1-5 (13), which translates materno-fetal barrier into sufficiently hampering SSTR1-5 functional response to octreotide.

Detection of SSTR-2 in the primary tumor of our patient is in accord with both the effectiveness of octreotide therapy, as well as its lack of detriment on the three fetuses, as assessed by their normal post–birth anthropometric measurements.

Seven cases in the literature have reported the safe and effective use throughout pregnancy of octreotide for treatment of nesidioblastosis, acromegaly and TSH-secreting pituitary macroadenoma. No deleterious effects on anthropometric measurements during pregnancy (10, 14), or breast feeding under octreotide treatment (9) were observed. Only one case reported low intrauterine growth (5–10th percentile) with no other unusual morphological features (12).

We present the first octreotide LAR use for the first case of carcinoid-associated Cushing’s syndrome during pregnancy ever reported. Additional case reports are needed to verify the safety of Octreotide and Octreotide LAR therapy during pregnancy.

Conclusions:

Our report demonstrates substantial addition to the safety of octreotide treatment throughout pregnancy, in addition to the seven previous case reports of safe octreotide (short- and long-acting preparations) therapy during pregnancy. Secondly, it supports the effectiveness of Octreotide LAR for bronchial-carcinoid EAS. Thirdly, it supports the correlation between good response to Somatostatin analogue
therapy, and the presence of SSTR-2 in the diseased target tissue. Fourthly, it demonstrates Octreotide LAR safe use throughout pregnancy, in regard to the anthropometric data of three babies, to the age of two years and more.

**Patient's perspective:**

"Soon after the disease remission I realized that I resumed my health. I felt powerful enough to challenge the illness and overcome it. Establishing a family was my desire and inspiration. In my opinion having and growing babies, is a clear declaration that I won the combat! I wanted to see them leaving to the kindergarten with bags on their shoulder, exactly the same way other mothers say "Bye bye" to their children. My father unconditionally supported me; he even stopped smoking for the sake of the first baby's health. The first success with treatment drove me to another two, thanks God. All I need is a routine visit to the clinic, and doing some analysis. So, what if all I need is a tiny injection every month!?"

**Abbreviations:**

ACTH: adrenocorticotropic Hormone.

EAS: Ectopic ACTH Secretion.

SSTR: Somatostatin-receptor.

SSA: Somatostatin Analogue.

**Consent:**

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

**Competing interest:**

“The authors declare that they have no competing interests”

**Authors' contributions:**

**DD:** attending physician in the outpatient clinic, attending endocrinologist while in-hospital, had drafted and edited the manuscript, obtained the patient's consent and perspective.

**AZ:** had searched previous relevant cases in the literature, reviewed and edited the article.

**ZSO:** had analyzed the lab. Samples obtained throughout investigation and follow up period.
MA: had performed the figures layout and reviewed the anthropometric data.

GK: had performed the somatostatin subtyping in pathological material.

AY: attending physician while hospitalized twice, during the course of her disease.

Acknowledgments

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References:


Illustration, tables and figures:

Figure 1. Anthropometric measures of the patient's three kids:

A. Body length, B. Head circumference, C. Body weight.

A. 

[Body length graph showing growth over age for the three children]

B. 

[Head circumference graph showing growth over age for the three children]

C. 

[Body weight graph showing growth over age for the three children]
Table 1. Patient's endocrine-biochemical laboratory tests

<table>
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* normal range 138-690 nmol/24 hr.

** normal range: 55-248 nmol/24 hr.

† normal range: 4.4-17.6 pmol/L. † †: 0-10 pmol/L.

‡ normal range: 1-84 mg/gr Creatinine.

Table 2. Data of patient's three pregnancies:

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