

Cushing's Disease in Pregnancy and Cabergoline Use: Obstetric and Neonatal Outcomes

Natacha B. Murillo¹, Constanza Ramacciotti¹, Carolina Fux-Otta^{2,3}, Laura A. Cecenarro^{1*}

¹Department of Endocrinology, Hospital Privado Universitario de Córdoba, Córdoba, Argentina

²Department of Endocrinology and Diabetes, National Maternity University Hospital, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina

³Hospital Translational Knowledge Unit (UCTH), National Maternity University Hospital, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina

*Corresponding author: Laura A. Cecenarro, laurycece@hotmail.com

Copyright: © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: Pregnancy in patients with Cushing's disease (CD) is rare and is associated with significant maternal and fetal complications. We report a case of CD who achieved uncomplicated pregnancy and delivery after treatment with low-dose cabergoline. A 29-year-old woman was diagnosed with CD (adrenocorticotrophic hormone-secreting macrotumor that causes displacement of the optic chiasm, infiltrates the right cavernous sinus, and engulfs the internal carotid artery) and underwent transsphenoidal surgery with incomplete tumor resection. After a year of clinical stability, her symptoms recurred, and cabergoline was initiated. During the treatment, the patient conceived, and the medication was suspended. In the first trimester, clinical and biochemical parameters indicate active CD, so cabergoline was reinstated at a low dose for the rest of the pregnancy. With the dopaminergic agonist, her clinical and laboratory parameters normalized, and the patient gave birth to a healthy girl at 38 weeks, within normal percentiles and without complications. Pregnancy in patients diagnosed with CD is a rare event, and the consequences of maternal-fetal exposure to hypercortisolism can be severe. Our experience with the use of cabergoline at low doses in a pregnant woman with CD contributes favorable data to the scarce existing literature reports, adding evidence on the safety profile of the drug in this population.

Keywords: Cabergoline; Cushing's syndrome; Pregnancy

Online publication: May 15, 2023

1. Introduction

Pregnancy in patients with Cushing's disease (CD) is extremely rare and is associated with significant maternal-fetal complications ^[1]. In such cases, it is important to control the cortisol level during gestation, either with surgical or pharmacological treatment, for favorable obstetric-neonatal outcomes ^[2]. We report a case of CD who achieved uncomplicated pregnancy and delivery upon treatment with low-dose cabergoline (CAB) for persistent hypercortisolism.

2. Case

A 29-year-old woman with history of hypothyroidism, arterial hypertension, menarche at age 18, and two uncomplicated pregnancies, sought medical attention in January 2018 for weight gain of 12 kg over a period of 1 year. On further history, we found that the patient also had oligomenorrhea, frequent headaches, and

emotional lability. On physical examination, her weight was 78 kg, height was 158 cm, body mass index (BMI) was 31.24 kg/m², and blood pressure (BP) was 110/75 mmHg; she had cushingoid facies, supraclavicular fat pad, globular abdomen with vinous-red striae, and dorsal hump. With suspicion of Cushing's syndrome (CS), investigations were done: morning plasma cortisol (Co AM) was 25.51 µg/dL [normal value (NV) < 22.5 µg/dL]; adrenocorticotropic hormone (ACTH) was 129 pg/mL (NV < 46 pg/mL); nocturnal salivary cortisol was 0.8 µg/dL (NV < 0.27 µg/dL); urinary free cortisol (UFC) was 290 µg/24 h (NV 20.9–292 µg/24 h); plasma cortisol level in dexamethasone suppression test was 11.9 µg/dL (NV < 1.8 µg/dL); and thyrotrophin (TSH) was 0.22 µUI/mL (NV 0.55–4.78 µUI/mL); other pituitary panel, glucose, electrolytes, and liver function were normal. Magnetic resonance imaging (MRI) of the pituitary reported a lesion of 30 mm in the greatest cephalo-caudal diameter in contact with and displacement of the optic chiasm, infiltrating the right cavernous sinus and encompassing the internal carotid artery (**Figure 1**).

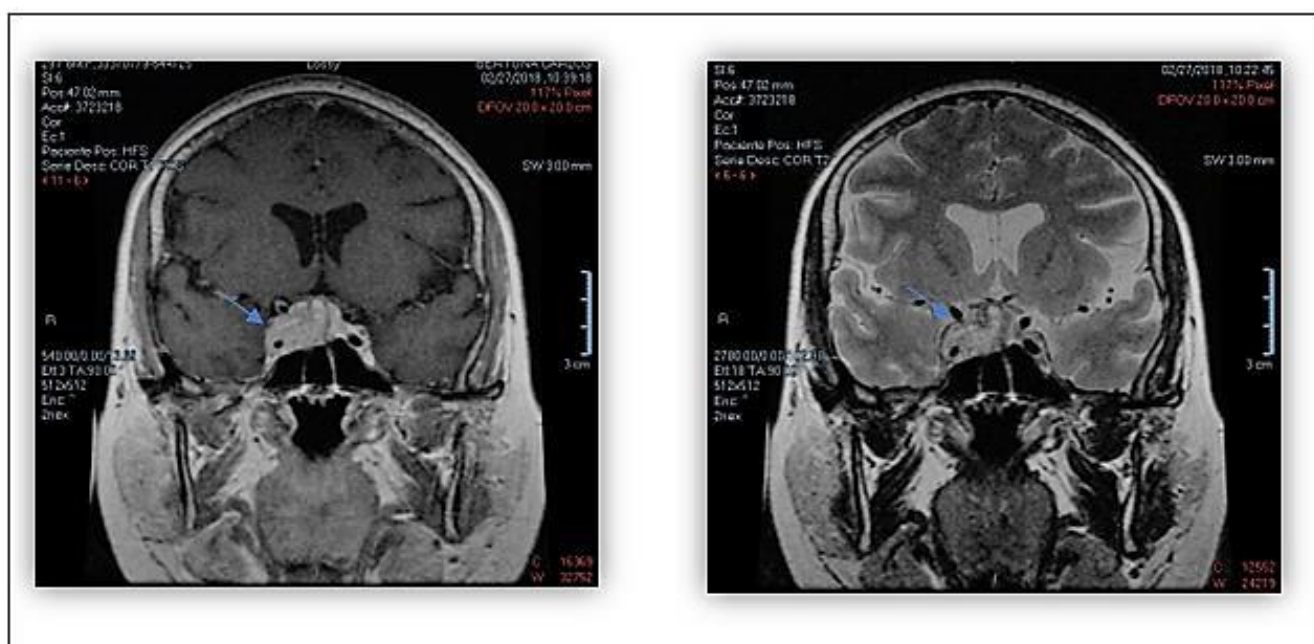


Figure 1. Nuclear magnetic resonance images of the sellar region. Coronal T1 (left) and T2 (right), showing pituitary microlesion, involving the right cavernous sinus and optic chiasm (blue arrows).

Given the diagnosis of ACTH-secreting pituitary macrotumor, ketoconazole was indicated, and she was referred to neurosurgery for surgical treatment. Transphenoidal surgery was performed in May 2018. The patient had a postoperative course without complications. On the fourth day after surgery, the AM cortisol was 2.81 µg/dL, without interference from exogenous glucocorticoids, so we decided to start her on hydrocortisone. The pathological findings were as follows: pituitary adenoma with ACTH expression and Ki-67 index of 10%, confirming the diagnosis of CD.

In the third month after surgery, MRI reported the following: decrease in size of the lesion located in sellar and suprasellar topography, leaving a small remnant at the level of the right cavernous sinus. The control computerized campimetry was normal, and the laboratory investigation of hormonal level was within the reference limits. The corticoid was gradually suspended. One year after surgery, the patient lost 15 kg, and her menstrual cycles became regular. However, her UFC and ACTH values increased progressively, so she was started on CAB 0.5 mg weekly (**Table 1**).

Table 1. Changes in biochemical parameters during follow-up

Timeline	AM cortisol ($\mu\text{g/dL}$) (NV 5–22 $\mu\text{g/dL}$)	Urinary free cortisol ($\mu\text{g/24 h}$) (NV 20.9– 292 $\mu\text{g/24 h}$)	Nocturnal salivary cortisol ($\mu\text{g/dL}$) (NV < 0.27 $\mu\text{g/dL}$)	ACTH (pg/ml) (NV < 46 pg/ml)
May 2018	7.21			35
June 2018		13.5	0.11	
December 2018	11.48	158	0.14	43.4
March 2019	1.54			
	(post-dexamethasone 1 mg)			
August 2019		478	0.13	
January 2020	11.94	155		69

She was prescribed with CAB intermittently for approximately 4 months but due to the diagnosis of pregnancy (despite insistence on the use of contraceptive methods), it was discontinued. During the first trimester, her UFC values increased (more than 2 times the NV), and oral glucose tolerance test (OGTT) was diagnostic for gestational diabetes. For this reason, CAB 0.5 mg/week was reintroduced during the second trimester, with hygienic-dietary measures and strict monitoring of blood glucose levels. The patient remained normotensive throughout the pregnancy, with improvement in UFC and OGTT without the need for insulin. Hence, the dose of the dopaminergic agonist (DA) was reduced by half. At 38 weeks of gestation, a baby girl was delivered by cesarean section with an APGAR score of 9/10. She was 3140 g (50th percentile), 47 cm in length (50th percentile), and had a head circumference of 35 cm (50th percentile). During puerperium, there were no complications, and her diabetes reclassification was normal. After delivery, CAB was suspended, and breastfeeding was maintained for 9 months. Subsequent controls showed elevated ACTH levels (72 pg/mL) and tumor remnant by MRI. Clinically, the patient had weight gain, the appearance of a hump, stretch marks, and headaches. Hence, radiosurgery was performed, with administration of a single dose of 22 Gy (Trilogy Linear Accelerator). Good clinical and biochemical results were observed 6 months after the intervention.

3. Discussion

CD is a rare condition with an incidence of 1.2 to 2.4 million per year in European studies and 6.2–7.6 million per year in the United States [3]. CD is characterized by a state of hypercortisolism caused by ACTH secretion from a pituitary neuroendocrine tumor. In women of childbearing age, hypercortisolism is associated with alterations of the reproductive axis, hypogonadism, and infertility, and if pregnancy occurs, there is greater maternal-fetal morbidity and mortality [2].

Caimari *et al.* [4] reviewed 263 pregnancies in patients with CS and found higher rates of gestational diabetes and pre-eclampsia in the group of patients with active CD versus the group with remission. In offspring, the following complications may occur: premature birth, intrauterine growth retardation, stillbirth, and fetal hypoadrenalism [5]. For these reasons, the management of CD during gestation should be early and comprehensive. However, diagnosis is a great challenge since the signs and symptoms of pregnancy overlap with those of the disease (fatigue, weight gain, hirsutism, emotional instability, stretch marks, and facial plethora) [6].

In pregnancy, physiologically, the hypothalamic-pituitary-adrenal axes and the renin-angiotensin-aldosterone system are activated, with a 2- to 3-fold increase in plasma cortisol levels as a result of elevated corticosteroid-binding globulin [7]. Nevertheless, the circadian rhythm of cortisol is maintained, which is why measurement of nocturnal salivary cortisol is recommended in most diagnostic protocols [8]. During

the second and third trimester, UFC also increases; therefore, UFC should not be considered a reliable marker after the first trimester, unless the increase is 2 to 3 times with respect to the NV [9].

In the case of our patient, we consider that pregnancy was achieved due to CAB treatment previously administered for persistent hypercortisolism secondary to post-surgical tumor remnant.

It is known that DAs restore the gonadal axis and fertility and their use in pregnant patients with prolactinomas has not demonstrated significantly greater adverse outcomes than those in the control population [10,11]. However, the experience with the use of CAB in CD during pregnancy is very limited, and for this reason, it was decided to discontinue AD and strictly control the clinical and biochemical parameters of the patient. The elevated UFC values in the first trimester and the diagnostic OGTT for gestational diabetes led us to resume treatment with low-dose CAB (0.5 mg/week), along with a dietary and physical activity plan adjusted to pregnancy. With these efforts, the clinical and biochemical parameters normalized, and thus the dose of AD was reduced by half. At 38 weeks, a cesarean section was performed, and a baby girl was delivered without complications.

Reports in literature on CAB treatment for CD during pregnancy are scarce compared to those of prolactinomas. Pivonello *et al.* [12] demonstrated the expression of dopaminergic receptors in corticotroph adenomas, thus hypothesizing that DAs induce the suppression of ACTH secretion and inhibition of cell growth. Although the treatment of choice is surgery, there is a percentage of persistence or recurrence of the disease; thus, medical and/or radiotherapeutic treatment should be considered as the second option. In our case, post-surgical remission could not be affirmed (despite the post-surgical cortisol level being lower than 3 µg/dL and the need for hydrocortisone replacement therapy) due to the tumor remnant in the cavernous sinus. Likewise, the history of macrotumor with Ki67 expression greater than 3% orients us to more aggressive lesions with worse prognosis [8]. In line with our experience, Nakhleh *et al.* [13] reported a case of CD in which the patient underwent non-curative pituitary surgery and conceived spontaneously four months after starting CAB, which was maintained at low doses throughout gestation; favorable outcomes were observed without evident complications [13]. Another similar case, reported by Sek *et al.* [14], describes a patient with CD treated with surgery and radiosurgery without achieving remission, and due to gestational desire, CAB was initiated, achieving spontaneous conception and pregnancy without complications [14].

Although there are other pharmacological options, not all available drugs have been shown to be safe, and some may even cause adverse events in mother and fetus. This is the reason they are contraindicated during pregnancy (**Table 2**) [5,15].

Table 2. Drugs used in the treatment of Cushing’s disease and their effects on pregnancy

Drug	Mechanism of action	Effect on pregnancy	References
Ketoconazole	Steroidogenesis inhibitor	Male fetus feminization	[15]
Mitotane	Adrenostatic and adrenolytic	Teratogenic	[15]
Metyrapone	Steroidogenesis inhibitor	Hypertension, preeclampsia, and preterm labor	[5]
Mifepristone	Glucocorticoid receptor antagonist	Abortifacient	[15]
Pasireotide	Somatostatin analog	Toxicity in animal reproduction studies	[15]

4. Conclusions

Pregnancy in patients with CD is a rare event. The consequences of maternal-fetal exposure to hypercortisolism can be severe. Our experience with the use of low-dose CAB in a pregnant woman with CD contributes favorable data to the scarce existing literature reports, adding evidence on the safety profile of the drug in this population.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

All authors were involved in conceptualization, data curation, and manuscript preparation, taking public responsibility for its content and approving its final version.

References

- [1] Sharma ST, Nieman LK, Feelders RA, 2015, Cushing's Syndrome: Epidemiology and Developments in Disease Management. *Clin Epidemiol*, 7: 281–293. <https://doi.org/10.2147/CLEP.S44336>
- [2] Laway BA, Mir SA, 2013, Pregnancy and Pituitary Disorders: Challenges in Diagnosis and Management. *Indian J Endocrinol Metab*, 17(6): 996–1004. <https://doi.org/10.4103/2230-8210.122608>
- [3] Broder MS, Neary MP, Chang E, et al., 2015, Incidence of Cushing's Syndrome and Cushing's Disease in Commercially-Insured Patients < 65 Years Old in the United States. *Pituitary*, 18(3): 283–289. <https://doi.org/10.1007/s11102-014-0569-6>
- [4] Caimari F, Valassi E, Garbayo P, et al., 2017, Cushing's Syndrome and Pregnancy Outcomes: A Systematic Review of Published Cases. *Endocrine*, 55(2): 555–563.
- [5] Lindsay JR, Jonklaas J, Oldfield EH, et al., 2005, Cushing's Syndrome During Pregnancy: Personal Experience and Review of the Literature. *J Clin Endocrinol Metab*, 90(5): 3077–3083.
- [6] Dong D, Li H, Xiao H, 2015, The Diagnosis and Management of Cushing Syndrome During Pregnancy. *J Obstet Gynaecol*, 35(1): 94–96.
- [7] Abou-Samra AB, Pugeat M, Dechaud H, et al., 1984, Increased Plasma Concentration of N-Terminal Beta-Lipotrophin and Unbound Cortisol During Pregnancy. *Clin Endocrinol (Oxf)*, 20(2): 221–228.
- [8] Ambroziak U, Kondracka A, Bartoszewicz Z, et al., 2015, The Morning and Late-Night Salivary Cortisol Ranges for Healthy Women May Be Used in Pregnancy. *Clin Endocrinol (Oxf)*, 83(6): 774–778.
- [9] Nieman LK, Biller BM, Findling JW, et al., 2008, The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 93(5): 1526–1540.
- [10] Fux Otta C, Cecenarro L, Estario ME, et al., 2015, Actualización en Endocrinología: Manejo de Las Prolactinomas Durante la Gestación [Update on Endocrinology: Management of Prolactinomas During Pregnancy]. *Rev Fac Cien Med Univ Nac Cordoba*, 72(3): 170–174.
- [11] Molitch ME, 2015, Endocrinology in Pregnancy: Management of the Pregnant Patient with a Prolactinoma. *Eur J Endocrinol*, 172(5): R205–R213.
- [12] Pivonello R, Ferone D, de Herder WW, et al., 2004, Dopamine Receptor Expression and Function in Corticotroph Pituitary Tumors. *J Clin Endocrinol Metab*, 89(5): 2452–2462.
- [13] Nakhleh A, Saiegh L, Reut M, et al., 2016, Cabergoline Treatment for Recurrent Cushing's Disease During Pregnancy. *Hormones (Athens)*, 15(3): 453–458.
- [14] Sek KS, Deepak DS, Lee KO, 2017, Use of Cabergoline for the Management of Persistent Cushing's Disease in Pregnancy. *BMJ Case Rep*, 2017: bcr-2016-217855. <https://doi.org/10.1136/bcr-2016-217855>

[15] Feelders RA, Hofland LJ, 2013, Medical Treatment of Cushing's Disease. J Clin Endocrinol Metab, 98(2): 425–438.

Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.