

Síndrome de Cushing ATCH-dependiente durante el embarazo tratado con metirapona

ACTH-dependent Cushing's syndrome during pregnancy treated with metyrapone

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ABSTRACT

Cushing's syndrome (CS) rarely occurs during pregnancy due to the influence of the hypercortisolism on the reproductive axis, with only a few cases described. We present a case of a 32 years-old woman diagnosed with ACTH-dependent CS and no clear pituitary lesion on the MRI. She was on ketoconazole when she discovered she was 8-weeks pregnant. Ketoconazole was stopped and a conservative management was decided. At 26 weeks of gestation, the patient developed gestational diabetes and treatment with metyrapone was started. Metyrapone was well tolerated and the pregnancy proceeded without further complications. She gave birth to a male infant, via cesarean section, at 36 weeks, with no apparent teratogenic effects of metyrapone. Many authors consider surgery as the first-choice treatment in pregnant women with CS but there is no consensus on the best management in such patients. Pharmacological treatment with metyrapone may be a safe and effective alternative.

Keywords: Cushing's disease; Pregnancy; Metyrapone.

Palabras clave: Enfermedad de Cushing; Embarazo; Metirapona.

INTRODUCTION

Cushing's syndrome (CS) is a rare disease in pregnancy because fertility is reduced, due to the hypercortisolism and/or hyperandrogenism^{1,2}. Hypercortisolism during pregnancy is associated with adverse maternal and fetal outcomes, such as arterial hypertension, gestational diabetes or glucose intolerance, heart failure, preterm labor and intrauterine growth retardation²⁻⁴. Because of its rarity in pregnancy, it remains a diagnostic and therapeutic challenge³. Surgical treatment is considered to be the most successful option^{1,5}, although treatment is usually individualized². Some pharmacological drugs, such as metyrapone and ketoconazole, are useful to treat CS in pregnancy⁴.

We present a case of a patient who presented with Cushing's disease that became pregnant in the setting of hypercortisolism and was treated during pregnancy with metyrapone.

CASE REPORT

A 32-year-old female was referred to Endocrinology due to severe hirsutism and central obesity. She had a history of non-intentional weight gain of 10 kg (body mass index of 36.6 kg/m²) and menstrual irregularities over the past 2 years. On examination, she had hirsutism (modified Ferriman-Gallwey Scale score of 15 points) and no florid signs of CS, namely facial plethora, acne, hyperpigmentation or striae. Etiological study was compatible with ACTH-dependent CS (Table 1). Pituitary magnetic resonance imaging (MRI) showed an asymmetry on the left side of the pituitary gland, which could correspond to a pituitary microadenoma (Figure 1). She underwent inferior petrosal sinus sampling, which confirmed left lateralization of the microadenoma. Treatment with ketoconazole 200mg daily was initiated and the patient was scheduled to a pituitary surgery.

A few weeks after treatment initiation, the patient discovered she was 8-weeks pregnant. Ketoconazole was stopped and

the case was discussed in an endocrine multidisciplinary team meeting, including Endocrinology, Obstetrics and Neurosurgery specialists. A decision of a conservative management was made considering the risks for both mother and fetus of transsphenoidal surgery during the first trimester and the lack of consistent evidence regarding medical treatment during pregnancy. She was kept under close antenatal surveillance and no complications were documented during the first trimester of pregnancy.

At 26 weeks of gestation, the patient was diagnosed with gestational diabetes following an abnormal oral blood glucose tolerance test and required medical treatment with metformin and glargine insulin. At this point, signs of hypercortisolism, Figure 1. Pituitary magnetic resonance imaging (MRI) showed an asymmetry on the left side of the pituitary gland, which could correspond to a pituitary microadenoma



Table 1. Biochemical results leading to diagnosis of Cushing's Disease

Plasma Measurements					
ACTH 8H: 51.5 pg/mL (reference range: 0-46)					
Cortisol 8H: 21.5 ug/dL (reference range: 6.2-19.4)					
Cortisol post 1 mg overnight dexamethasone suppression test: 14.1 ug/dL (reference: <1.8)					
Cortisol post combined low-dose dexamethasone-CRH test: 26.1 ug/dL (reference: <1.4)					
Urine Measurements					
Free urinary cortisol: 555.7 ug/24H (reference range: 20-90)					
Bilateral inferior petrosal sinus (IPS) sampling for ACTH levels (pg/mL)					
Reference for localization: pituitary/periphery ratio >2 and >3 after CRH. Reference for lateralization: higher side/lower side ratio > 1.4					
Time	Right IPS	Left IPS	Peripheral	Ratio pituitary/periphery	Ratio left/right
0'	38,8	161,0	31,7	5.1	4.1
3'	116,0	>1250,0	47,6	26.3	10.8
5'	110,0	637,0	92,2	6.9	5.8
10'	110,0	1087,0	89,5	12.1	9.9
15'	113,0	>1250,0	86,5	14.5	11.1

such as striae, became more apparent. She was normotensive and there was a normal development of the fetus, with no obstetric complications. Cushing's treatment options were again discussed in an endocrine multidisciplinary team meeting. The risks associated with pituitary surgery during pregnancy, for both mother and fetus, were considered to be higher than the likelihood of surgical cure, in view of the size and the location of the microadenoma. Therefore, it was decided not to intervene surgically. Because of the risks of hypercortisolism, pharmacological treatment was decided and, at the 27th week of gestation, the patient started taking metyrapone 250mg four times a day, with dose titration every three weeks.

Metyrapone was well tolerated, with no side effects apart from slight exacerbation of the hirsutism. There was a decrease in 24-hour urinary free cortisol levels (until 2-times the upper limit) following treatment with metyrapone (Graphic 1).

She remained normotensive during pregnancy, blood glucose levels were within range with medication and there were no apparent fetal complications. She gave birth to a male infant via cesarean section following premature rupture of membranes at 36 weeks of gestation. The child weighted 3380 grams and had APGAR score of 5 at 1 minute, 8 at 5 minutes and 10 at 10 minutes. The newborn's progress was uncomplicated and no adverse fetal effects of metyrapone treatment were apparent. In the postpartum period, blood glucose levels were within normal range without medication and the patient remained normotensive. There were no maternal complications apart from the healing of the caesarian section, which was impaired and required treatment with vancomycin following the development of cellulitis.

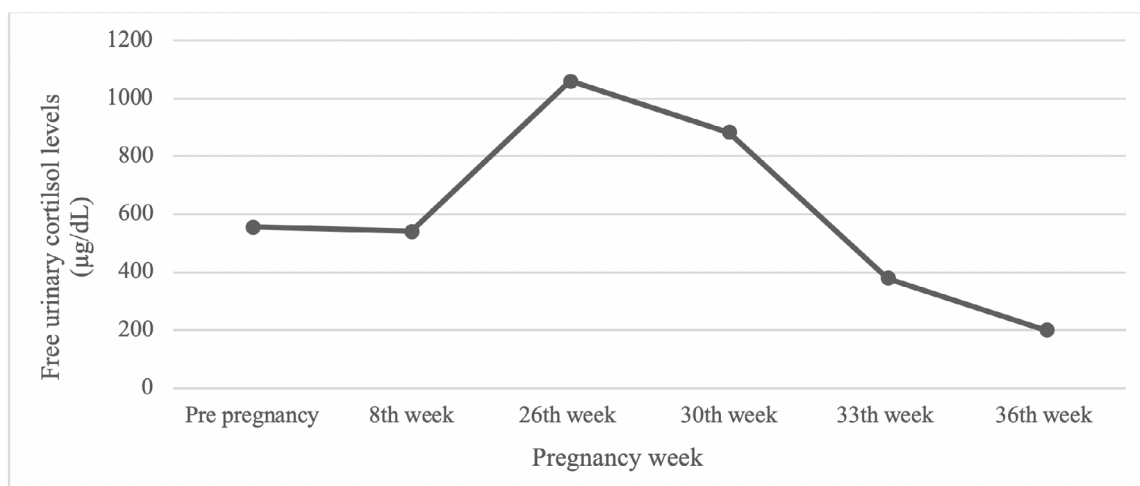
Maternal urinary cortisol excretion increased following delivery, requiring an increase in the dose of metyrapone up to 3000 mg daily. She underwent transsphenoidal surgery and histopathology confirmed a corticotroph adenoma with tumor cells showing a positive staining for ACTH, LH and prolactin.

Morning serum cortisol levels following pituitary surgery were 13.8 µg/dL, suggesting maintenance of the disease.

DISCUSSION

CS is a rare disease in pregnancy as hypercortisolism and hyperandrogenism suppress the gonadal axis and ovulatory disorders are common^{1,2,6}. The first published case of Cushing's syndrome in pregnancy was reported by Hunt and McConeahey in 1953⁷, with fewer than 200 cases described in the literature³. Contrary to non-pregnant patients, where the most common cause of CS is a pituitary adenoma (70%), in pregnancy the incidence of adrenal adenomas is about 60% whereas pituitary disease accounts for only a third of the cases⁴. Due to physiological changes in the hypothalamic–pituitary–adrenal axis, results of hormonal tests during pregnancy are difficult to interpret, and the diagnosis of CS during pregnancy is remarkably challenging. During pregnancy, corticotropin-releasing hormone (CRH) and ACTH plasma levels increase in the first trimester due to placenta production^{4,8}. This results in an elevation of serum, salivary and urinary cortisol levels, but the cortisol secretion maintains its circadian rhythm through the pregnancy⁸. Even taking into account the increase of corticosteroid-binding globulin (CBG) due to high levels of estradiol during pregnancy, which falsely increases serum cortisol levels, serum-free cortisol levels increase during pregnancy by the 11th week about 1,6 fold and urinary free cortisol levels increases up to threefold the normal range^{4,8}. It is very important to take these physiological changes into account in order to make a correct diagnosis of CS during pregnancy. Moreover, they are particularly significant during monitoring of treatment of a pregnant woman with CS, once aiming to normalize cortisol levels in pregnancy with pharmacological treatment could result in hypocortisolism of the fetus. Because of the rarity of this condition, with few cases reported, definite conclusions and recommendations for the

Graphic 1. Excretion of free cortisol levels in 24h urine sample during pregnancy
(normal range in non-pregnant women 20-90 µg/24h)



best management for CS during pregnancy are not available². The chosen approach is usually individualized, depending on the etiology of CS, the severity of hypercortisolism and the pregnancy stage². Equally to non-pregnant women, surgery is the definite treatment in pregnant CS patients and endoscopic transsphenoidal approach or adrenalectomy, ideally between the 12th and 29th weeks of gestation, is often recommended as the first treatment option^{1,2,5}. Nonetheless, it is described that most pregnant women with CS didn't receive any specific treatment during pregnancy². In women who were treated during pregnancy, the main treatment of CS was indeed surgery, but as previously mentioned, most cases during pregnancy are adrenal disorders and, to our knowledge, there are only twelve published case reports of transsphenoidal surgery for CD during pregnancy⁹. Taking into account the possible adverse outcomes of pituitary surgery, which is associated with more morbidity and inferior rates of surgical cure compared to adrenalectomy, the patient in our case was treated with transsphenoidal surgery only after the delivery.

When surgery is not possible or contraindicated, conservative medical treatment with steroidogenesis inhibitors are an option in order to control the hypercortisolism and prevent complications⁴. In literature, the most commonly used drug is metyrapone, in 70% of cases, followed by ketoconazole in 15%, aminoglutethimide in 3%, cyproheptadine in 6%, cabergoline in 3%, and mitotane in 3%². In our case, metyrapone was chosen to control the hypercortisolism, starting in the second trimester of pregnancy following the development of gestational diabetes. Although there aren't any available studies in pregnancy, metyrapone seems to be a safe alternative to surgery in the control of hypercortisolism, with only one case described of fetal hypoadrenalism^{4,10}. Metyrapone inhibits the last step in cortisol biosynthesis through inhibition of the 11-beta hydroxylase enzyme and the main precautions are due to the adverse effects of the increased levels of 11-de-

oxycorticosterone, which can cause hypokalemia, edema, hypertension and progression to eclampsia^{1,4}. However, these side effects are infrequent and the dose should be tampered until urinary cortisol levels are reduced to the upper limit of the observed in normal pregnancy^{4,10}. Ketoconazole, a well-known antifungal agent, is less used during pregnancy because it crosses the placenta and has teratogenic and anti-androgenic effects in animal studies⁴. For these reasons, treatment with ketoconazole was stopped once the pregnancy was confirmed. However, teratogenic and anti-androgenic effects of ketoconazole had not been described in humans and this drug has been used successfully in pregnancy without significant side effects^{11,13}. In our case, the patient was medicated with ketoconazole during the first weeks of pregnancy, a period in which there is important embryonic development, and no teratogenicity was noted.

Corticotroph pituitary adenomas may express functional dopamine receptors and cabergoline, a dopamine agonist used in the treatment of hyperprolactinemia, has showed to be effective controlling cortisol secretion in nonpregnant patients¹⁴. Most studies regarding cabergoline treatment during pregnancy didn't show any increase of adverse pregnancy outcomes, however, the majority of studies refer to treatment with low doses of cabergoline and doses used in the treatment of CD are much higher than those used in the treatment of hyperprolactinemia^{14,15}. As there are few reports of patients with CS treated with dopamine agonists during pregnancy, cabergoline was not our choice of treatment.

Pregnancy in patients with CS is associated with maternal and fetal complications^{2,4}. In our case, our patient remained normotensive throughout the pregnancy, even after metyrapone was started, but developed gestational diabetes that required pharmacological treatment. Moreover, she had a preterm delivery at the 36th week of gestation and presented with abdominal cellulitis following the caesarian section.

As CD is pregnancy is rare, there is no consensus on its best management². We initially opted to manage this patient conservatively by trying to control comorbidities without using specific anti-cortisol drugs, as large studies regarding its safety during pregnancy are not available. We also opted not to perform pituitary surgery during pregnancy, after a multidisciplinary discussion with Obstetrics and Neurosurgery specialists considered the therapeutic risk-benefit for the maternal-fetal outcomes to be unfavorable. The question whether earlier pharmacological treatment or a surgical approach during pregnancy could have prevented the development of gestational diabetes or preterm labor remains; however, even in treated cases, some patients still develop complications, such as premature delivery⁴. We believe that treatment with metyrapone, initiated during the second trimester of pregnancy, reduced hypercortisolism and prevented the development of further complications. Moreover, the newborn's progress following delivery was uncomplicated and no teratogenic effects were noted.

CONCLUSION

Cushing's disease rarely occurs in pregnancy^{1,2}. Hypercortisolism negatively impacts on the prognosis of pregnancy and is associated with adverse maternal and fetal outcomes^{2,4}.

Validated guidelines regarding treatment of Cushing's disease during pregnancy are not available so management is usually individualized². As in non-pregnant women with CS, surgery is considered to the first-line treatment and medical treatment is reserved for situations where surgery is not possible or is contra-indicated^{1,2,5,5}. Currently, metyrapone represents the best pharmacological treatment³.

In our case, treatment with metyrapone was a safe alternative to surgery and prevented the development of further complications. As CD is rare in pregnancy, therapeutic decisions should be made by a multidisciplinary team consisting of Endocrinology, Obstetrics and Endocrine Neurosurgery specialists.

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