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CASE REPORT

IATROGENIC CUSHING'S SYNDROME AS A CONSEQUENCE OF NASAL USE OF BETAMETHASONE SPRAY DURING PREGNANCY

A. Scutelnicu[1], A.M. Panaitescu[1,*], A.M. Ciobanu[1], N. Gica[1], R. Botezatu[1], G. Peltecu[1], M.L. Gheorghiu[2,3]

[1]"Filantropia" Clinical Hospital of Obstetrics and Gynecology, [2]"C.I.Parhon" National Institute of Endocrinology - Neuroendocrinology, [3]"Carol Davila" University of Medicine and Pharmacy - Endocrinology, Bucharest, Romania

Abstract

Introduction. Glucocorticoids (GC) are largely used for their anti-inflammatory and immunosuppressive effects. Until recently "local" administration (inhalation, topical, intra-articular, ocular and nasal) was considered devoid of important systemic side effects, but there is no administration form, dosing or treatment duration for which the risk of iatrogenic Cushing's syndrome (CS) and consequent adrenal insufficiency (AI) can be excluded with certainty.

Patients and methods. We present the case of a pregnant woman who developed overt CS with secondary AI in the second trimester of pregnancy. She had low morning plasma cortisol 6.95 nmol/L (normal non-pregnant range 166 – 507) and low ACTH level 1.54 pg/mL (normal range 7.2 – 63.3), suggestive for iatrogenic CS. A thorough anamnesis revealed chronic sinusitis long-term treated with high doses of intranasal betamethasone spray (6 - 10 applications/day, approximately 10 mg betamethasone/week, for 5 months). After decreasing the dose and switching to an alpha-1 adrenergic agonist spray, the adrenal function recovered in a few weeks without manifestations of AI. The patient underwent an uneventful delivery of a normal baby. A review of the literature showed that only a few cases with exogenous CS and consequent AI caused by intranasal GC administration were described, mostly in children, but none during pregnancy.

Conclusion. Long-term high doses of intranasal GC may induce iatrogenic CS and should be avoided. Low levels of ACTH and cortisol should prompt a detailed anamnesis looking for various types of glucocorticoid administration.

Keywords: Iatrogenic Cushing's syndrome, nasal betamethasone, adrenal insufficiency, pregnancy.

INTRODUCTION

Cushing's syndrome (CS) during pregnancy is rare (around 220 reported cases) probably because hypercortisolism suppresses gonadotropin secretion and leads to amenorrhea or oligomenorrhea and anovulation (1,2). Benign adrenal adenoma is the most common cause of endogenous CS in pregnant women (in 40-60% of cases), in contrast to non-pregnant women where the most frequent cause is Cushing's disease, while adrenal adenomas account for only 10-15% of cases (1-3). Lindsay and Nieman (3), reviewing 136 pregnancies in 122 women with CS, described the following causes: adrenal adenoma (n=56); Cushing's disease (n=40); adrenal carcinoma (n=12); ectopic corticotropin secretion (n=4); corticotropin-independent hyperplasia (n=4) - possibly due to atypical receptor stimulation and Carney complex (n=1). Exogenous (iatrogenic) CS usually develops with oral administration of glucocorticoids (GC) for chronic inflammatory disease such as inflammatory bowel disease, polymyalgia rheumatica and/or giant cell arteritis, rheumatoid arthritis, systemic lupus erythematosus or vasculitis (4). Until recently "local" administration (inhalation, topical, intra-articular, ocular and nasal) was considered devoid of important systemic side effects, but recent evidence shows that there is no administration form, dosing or treatment duration for which the risk of iatrogenic CS and secondary adrenal insufficiency (AI) can be excluded with certainty, although higher doses and longer use give the highest risk (5).

Misdiagnosis of CS is common in pregnancy, as symptoms suggesting CS overlap with those commonly seen in pregnancy such as weight gain, abdominal striae, hypertension, fatigue, hyperglycemia, emotional challenges, preeclampsia or gestational diabetes mellitus. However, the presence of ecchymosis, myopathy, wide, red, diffuse striae, difficult to control high blood pressure and hyperglycemia in diabetes mellitus should alert the clinician towards a possible CS (1).

CS during pregnancy can be associated with severe maternal complications such as hypertension or

*Correspondence to: Anca Maria Panaitescu MD, "Filantropia" Clinical Hospital of Obstetrics and Gynecology, 11 Ion Mihalache Blvd., Bucharest, 011161, Romania, E-mail: panaitescu.anca@yahoo.com

preeclampsia, diabetes or impaired glucose tolerance, poor wound healing, osteoporosis, fractures, severe psychiatric complications, cardiac failure or even death (2,6). Fetal complications include early spontaneous abortion, prematurity, stillbirth, intrauterine growth restriction, hypoadrenalism (1,2,6,7). Therefore, a rapid diagnosis of CS and its cause during pregnancy, although difficult due to the physiological hypercortisolic state of the pregnancy, is extremely important, allowing timely treatment and improved prognosis. Surgery is the mainstay of treatment in women with endogenous CS during pregnancy, since most of the medical therapies (except cabergoline for Cushing's disease) may have toxic or teratogenic effects upon the fetus (8).

In this paper we present the case of a pregnant woman with iatrogenic CS due to high doses of intranasal betamethasone spray administration. A review of the literature (Medline, PubMed, and Google) was also undertaken for nasal GC administration and CS or secondary AI.

CASE REPORT

A 30-year-old pregnant woman G1P1, at 23 weeks of gestation was referred to an endocrinologist for excessive weight gain of 22 kg mainly in the last 2 months, associated with important lower leg edema, moderate facial and arm edema, wide red-violaceous striae on both lumbar regions, hips and internal thighs (Fig. 1), a round facies and chronic fatigue.

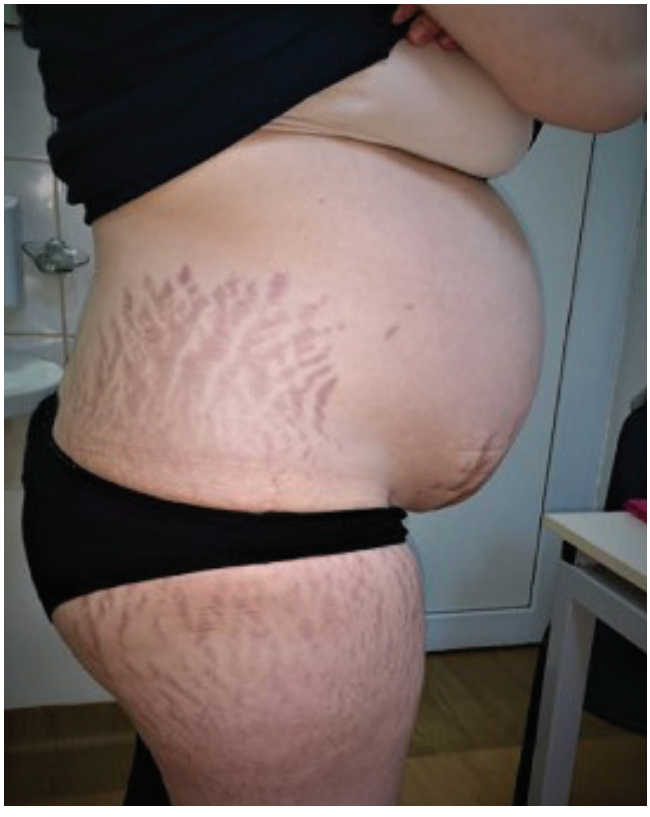

Figure 1. Patient at 39 weeks of pregnancy with red violaceous striae.

She had central obesity with a body mass index of 28.73 kg/m^2 (while before pregnancy it was 21.29 kg/m^2); blood pressure was 110/75 mmHg (personal history of 130/80mmHg as maximum value) and pulse 72 beats per minute. She had no current headaches, no hirsutism, the visual field was normal. The rest of the cardiovascular, respiratory and neurological examination was normal.

The patient had been diagnosed with left frontal sinus hypoplasia and chronic rhinosinusitis 5 years before, when she had multiples episodes of acute frontal headaches. She had been on chronic treatment with xylometazoline nasal spray (a sympathomimetic drug) for important nasal obstruction that impacted the quality of life and sleep. At the beginning of the pregnancy, her nasal drops were replaced with betamethasone nasal spray, which is permitted during pregnancy if used with caution. She used 2 vials of betamethasone spray per week (up to 8-10 applications/day), for 5 months, resulting in 10 mg of betamethasone/week. The patient was also known with chronic autoimmune thyroiditis and normal thyroid function tests during pregnancy (fT4=11.1 pmol/L and TSH=2.0 uUI/mL).

Laboratory evaluation showed high fasting glucose level of 124 mg/dL, high cholesterol level (313 mg/dL) with high LDL-cholesterol (202 mg/dL), mild leukocytosis with neutrophilia, normal coagulation screen, normal electrolytes, liver enzymes and renal function screen. According to the current screening recommendations in Romania (9,10), the patient undertook a modified oral glucose tolerance test and was diagnosed with gestational diabetes mellitus in the second trimester of pregnancy; diet with close self-monitoring of fasting glucose, at 1 and 2 hours post-prandial were recommended.

A brief hormonal screening showed a very low morning plasma cortisol – 6.95 nmol/L (0.25 µg/dL) (normal range in the 2nd trimester of pregnancy = 2 times higher than the non-pregnant range of 166-507 nmol/L), with a low ACTH level of 1.54 pg/mL (normal non-pregnant range 7.2 – 63.3 pg/mL), suggesting central adrenal insufficiency (AI) – see Table 1 (3,11,12,13). Abdominal ultrasound revealed normal adrenal glands with no nodular masses. Fetal ultrasound and biophysical profile were normal.

Taking into account the Cushingoid features and the laboratory tests showing low morning cortisol

and ACTH levels, without clinical signs of pituitary insufficiency, the diagnosis was iatrogenic Cushing's syndrome in pregnancy secondary to the use of intranasal betamethasone spray. The patient was advised to replace it with iso- or hypertonic seawater spray and then to start replacement therapy with oral hydrocortisone 15 mg/day in order to prevent the clinical manifestation of AI secondary to the betamethasone-induced ACTH suppression. However, the patient continued only with a reduced dose of the betamethasone nasal spray (about 0.3- 0.5 mg/day) for about 1 week, then switched to an alpha-1 adrenergic agonist spray for the rest of the pregnancy, without any symptoms of AI.

When she was reevaluated at 30 weeks of gestation, the patient was in much better shape, with no more excessive weight gain, she was feeling more active and energetic, with the same aspect of the striae while the lower-leg edema was less noticeable. The hormonal evaluation undertaken 5 weeks after bethametasone withdrawal revealed overall improvement of the adrenal gland suppression with high-normal morning ACTH level (63.36 pg/mL, which is normal for the 3rd trimester of pregnancy), improved serum cortisol level - 253 nmol/L (9.1 μg/dL), but still somewhat below the normal range in pregnancy (which is 2 to 3 times the normal non-pregnant range of 133 – 537 nmol/L), low 24 hour – urinary free cortisol (UFC) - 90.72 nmol/24h (normal values are 2-3 times the non-pregnant range of 100-379 nmol/24h). Gestational diabetes remained well controlled under diet, with glucose levels below recommended threshold values, without requiring insulin supplementation. Blood pressure and other signs suggestive of hypertensive complications such as preeclampsia were carefully monitored and normal parameters were recorded throughout gestation.

The patient was admitted at 39 weeks of gestation for an induction of labor which was carried out uneventfully and a 3500 g male baby was delivered without peripartum or neonatal complications. Three months after delivery the patient had normal non-pregnant levels of serum cortisol, ACTH and UFC.

DISCUSSION

Cushing's syndrome during pregnancy is rare. Diagnosing CS in this instance is usually complicated by the large overlap of many of its clinical signs and symptoms with those of normal pregnancy and by the physiological state of hypercortisolism that characterizes normal pregnancy. Weight gain, abdominal striae, hypertension, fatigue, hyperglycemia and emotional challenges are features of both normal pregnancy and CS. However, the presence of ecchymosis, easy bruising, proximal myopathy, wide, red purple, diffuse striae, facial plethora, osteoporosis, difficult to control high blood pressure and hyperglycemia in diabetes mellitus are not common in pregnancy and should alert the clinician on the possibility of CS. In our patient, the

Table 1. Reference ranges for cortisol and ACTH secretion during normal pregnancy (adapted from 3, 11-13)

Assay/Method	**Non-pregnant women**	**1st trimester**	**2nd trimester**	**3rd trimester**
Morning total plasma cortisol	13.2 ± 1.0 μg/dL	20.9 ± 1.1 μg/dL	31.8 ± 1.0 μg/dL	37.8 ± 1.5 μg/dL
LC-MS/MS (11)	364 ± 19 nmol/L	577 ± 30 nmol/L	878 ± 28 nmol/L	1043 ± 41 nmol/L
Mean increase*	-	1.5 x	2.0 - 2.4 x	2.5 - 2.8 x
Plasma free cortisol				
LC-MS/MS (11)				
Mean increase	-	1.2 x	1.4 x	1.6 x
Morning salivary cortisol	Large variation			
Immunoassays	between methods			
Mean increase (13)	-	1.0 x	1.06 – 1.6^ x	1.18 – 2.5^ x
Late-night salivary cortisol (13)	0.03 – 0.13 μg/dL	0.03 – 0.25 μg/dL	0.04 – 0.26 μg/dL	0.07 – 0.33 μg/dL
Elisa Immunoassay	0.8 – 3.6 nmol/L	0.8 - 6.9 nmol/L	1.1 - 7.2 nmol/L	1.9 - 9.1 nmol/L
Mean increase	-	1.1 x	1.4 x	2.1 x
24h- Urinary free cortisol	78 ± 12 nmol/day	135 ± 10 nmol/d	187±13 nmol/d	242±15 nmol/d
LC-MS/MS (11)				
Mean increase		1.7 x	2.4 x	3.1 x
Plasma ACTH	-	23 ± 4.6 pg/mL	NA	59± 16 pg/mL
RIA (12)		(12 week)		(37 week)
Low dose dexamethasone suppression test (3)		Less than 40% have normal suppression (cortisol < 1.8 μg/dL, 50 nmol/L)		

Legend: LC-MS/MS = Liquid chromatography/mass spectrometry; immunoassays may show higher values of UFC (particularly in unextracted samples) and lower values of total cortisol compared to the gold standard LC-MS/MS; *mean increase during pregnancy compared to non-pregnant women; ^ increasing values during pregnancy have been shown by some, but not all authors (see Langlois).

obstetrician suspected CS based on the excessive weight gain, puffy edema of the face and legs, reported chronic fatigue and wide purple striae with atypical distribution compared to what is normally seen in pregnancy.

During pregnancy, specific metabolic and endocrine changes along with the contribution of the placenta interfere significantly in the cortisol's metabolism, making the diagnosis of CS a real challenge. The hypothalamic-pituitary-adrenal axis (HPA) is overactive in pregnancy (Fig. 2); there is a progressive rise in serum, salivary and UFC, reaching levels seen with CS in non-pregnant state (Table 1) (1-3, 11-13). Serum and UFC cortisol levels increase from early 2nd trimester to about two- or three-fold in the 2nd and 3rd trimester, compared with nonpregnant women (11). Night salivary cortisol increases 2-fold in the 3rd trimester compared to nonpregnant women (14). The rise in placental estrogen increases the hepatic production of cortisol-binding globulin (CBG) – rising up to 3-fold in the 3rd trimester, which contributes to the increased circulating levels of total cortisol (11, 12). The circadian rhythm of cortisol production seems to be preserved, although it can be partially blunted (15). There is less dexamethasone suppression than in non-pregnant women (1, 3).

ACTH plasma level also rises during pregnancy to slightly above normal despite the increase in cortisol; it may be lower than in non-pregnant state in early pregnancy (Table 1). ACTH increase in pregnancy is thought to be due to multiple factors, including production in the placenta of similarly acting substances to CRH and ACTH, desensitization of the pituitary to the cortisol feedback and enhanced pituitary response to substances such as vasopressin that may induce corticotropin release (16). The current guidelines recommend several tests to be used as first-line for the diagnosis of CS: late night salivary cortisol, 24 hours UFC and the overnight 1mg or 2mg/48 hours dexamethasone suppression tests; however, the normal values are not well-validated for pregnancy, therefore diagnosing CS in pregnancy is difficult (17).

Fortunately, most cases of CS in the non-pregnant state, but also during pregnancy are iatrogenic from medically prescribed GC (exogenous CS), as it

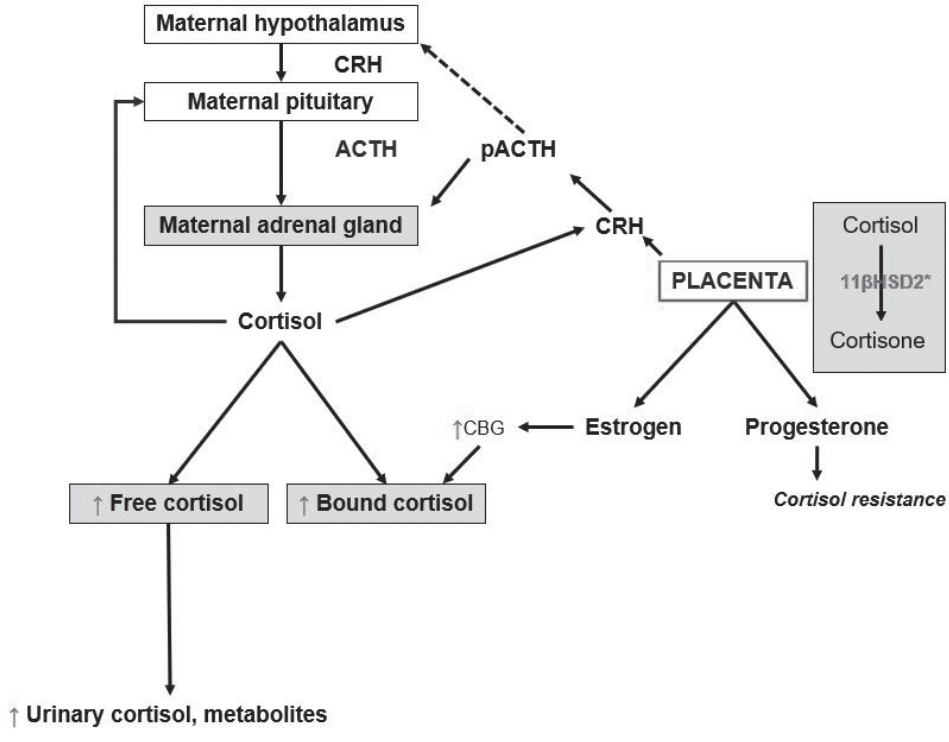

Figure 2. Interaction changes in the HPA axis in pregnancy. Plasmatic levels of total and free cortisol increase during pregnancy. Estrogen produced by the placenta increases hepatic production of cortisol-binding globulin (CBG) with consequent increase in total serum cortisol. Also, there is an increased production during pregnancy of corticotropin-realising hormones and adrenocorticotropic hormone (pACTH) by the placenta and they act by supplementary increasing total and free serum cortisol levels. During pregnancy the adrenal glands are more sensitive to ACTH and progesterone seems to increase the resistance to cortisol. All these changes make pregnancy a state of hypercortisolism. The fetus is protected by inactivation of maternally derived cortisol to cortisone by placental 11-b-hydroxysteroid dehydrogenase 2 (11βHSD2).

was the case in our patient.

Unlike the endogenous CS that is characterized by an increased serum cortisol and UFC, in the iatrogenic CS cortisol levels are usually low to undetectable when the patient takes any glucocorticoid except hydrocortisone. ACTH may be suppressed in the iatrogenic CS through the negative feedback exerted by the high levels of serum glucocorticoids upon the hypothalamic CRH- and pituitary ACTH- secreting cells (3, 18, 19). As a consequence, the adrenal glands and their cortisol secretion become gradually suppressed and a central AI installs in a time and dose-dependent manner, while the mineralocorticoid production is not affected as it is dependent on the renin-angiotensin system (20).

Adrenal suppression depends upon the potency of GC preparation used, its dose, route and duration of administration (4,5). It should be anticipated in any patient taking the equivalent of 7.5 mg prednisolone/ day for over 3 weeks (4, 21).

Our patient had an iatrogenic CS with secondary (central) AI due to long-term intranasal administration of high doses (10 mg/week) of betamethasone spray, a potent corticosteroid with a long duration of action (half life >36 hours). For comparison, a similar injectable dose would be equivalent to 11.8 mg oral prednisolone or prednisone/day) (22).

The GC-induced adrenal suppression is reversible in the great majority of cases after careful and gradual withdrawal of the steroids, but full recovery of the adrenal function may take up months after GC cessation. Sudden cessation of treatment may result in anorexia, nausea, vomiting, abdominal pain, adrenal crisis and even death (4, 23). Though considered rare with oral or inhaled preparations, the possibility of the occurrence of adrenal crisis should always be kept in mind in those taking GC (24).

The diagnosis of secondary AI in pregnancy has also its challenges. Basal serum cortisol, plasma ACTH and the 250 μg cosyntropin test are currently the tests of choice (13), but with higher cut-offs than in non-pregnant women. A morning basal serum cortisol level of ≤ 3.0 μg/dL is indicative of AI (25); however, in a suggestive clinical context, a short cosyntropin test should be considered when cortisol values are > 3 μg/dL but below 11, 16.3, and 22 μg/dL during the 1st, 2nd, and 3rd trimesters, respectively (26), or even for values below 25 – 32 μg/dL (13, 25). Higher peak serum cortisol cutoffs during cosyntropin stimulation test have been suggested for diagnosing AI, e.g., 25, 29 and 32 μg/dL during the 1st, 2nd and 3rd trimesters of pregnancy, instead of 18 μg/dL (26). Although cosyntropin is a category C drug in pregnancy, one dose during testing is unlikely to have significant side-effects (13, 25). Salivary cortisol reference ranges for AI are still to be validated. The insulin tolerance test is not recommended because of potential harm to the fetus (26). When a pituitary tumor is suspected as the cause of AI, non-contrast pituitary MRI may be (rarely) indicated in pregnancy (25).

Our patient had very low morning plasma cortisol and ACTH levels during the 2nd trimester of pregnancy, consistent with secondary AI, therefore no cosyntropin stimulation test was performed.

Patients with a suppressed HPA axis may develop an adrenal crisis if steroids are stopped or not increased during an acute illness, therefore they should be evaluated and receive stress dose steroids (4, 5). If possible, the GC treatment may be progressively weaned and the adrenal function monitored until normalization. Our patient stopped treatment rapidly (after 1 week of dose reduction) and did not take the prescribed hydrocortisone replacement dose. Five weeks after GC withdrawal, the patient showed improved but still lower than normal serum cortisol and UFC levels, however with a significant clinical improvement and no symptoms of AI. This was probably due to an incomplete adrenal suppression.

Nasal steroid preparations have been used for many years for the treatment of allergic and non-allergic nasal symptoms (eg rhinitis, rhinosinusitis, rhino-conjunctivitis and nasal polyposis). They now account for one of the most common ENT prescriptions and are regarded as exceptionally safe, including during pregnancy, usually with no side-effects when used nasally (5,27). Direct absorption of steroids through the nasal and respiratory mucosa is usually small (27). However, they may be absorbed from the gastrointestinal tract into systemic circulation after they have been swallowed, nasal drops being more likely to be swallowed than nasal spray (28,29). Most studies have shown no evidence of significant HPA axis suppression from nasal steroid use (27).

A review of the literature revealed only a few published cases of exogenous CS or secondary AI from intranasal prolonged use of nasal GC, none in pregnant women. In adults 10 cases of induced CS were described in patients taking nasal GC, either dexamethasone or betamethasone (23,29-37), and more than 15 cases have been described in children (28,38-44). Clinically manifest CS was described more frequently in children than in adults.

In previously reported cases of iatrogenic CS with nasal dexamethasone administration, the systemic effects developed after a longer period than in our patient (average of 3 years) and with doses of 4.5 to 9 mg dexamethasone per day (27). In children, CS was described after 2 – 3 months of treatment (40). Suppression of the HPA axis from betamethasone drops was reported after at least one year of administration and a dose equivalent to prednisolone ranging from 3 mg to 20 mg/day (23,33,36), but also after only 6 weeks of treatment (35). Unlike dexamethasone and betamethasone, beclomethasone is considered safer in local administration due to a smaller effective dose required and rapid inactivation by the liver if swallowed. Therefore, systemic side effects may appear only after high doses, up to 8 mg per day which is equivalent to 160 intranasal puffs per day, or after a longer period of more than 6 years (29). Newer steroid compounds administered intranasally, e.g. fluticasone proprionate or furoate and mometasone furoate, have a very low absorption rate and were not found to produce alterations to the HPA axis (45-47).

In a recent meta-analysis of 74 studies, HPA axis suppression in mostly adult (over 12 years old) patients using corticosteroids was seen in 4.2% of 173 patients with nasal administration (95% CI 0.5–28.9%), in 7.8% of those taking inhaled corticosteroids (95% CI 4.2–13), compared to 4.7% (95% CI, 1.1–18.5) for topical administration, 52.2% (95% CI, 40.5–63.6) for intra-articular corticosteroids and 48.7% (95% CI, 36.9–60.6) after oral administration (5). The diagnosis of AI was established by a cortisol level ≤ 500 nmol/L after stimulation tests with insulin, ACTH, CRH or metyrapone. Overall, the prevalence of AI is proportional to the dose and the treatment duration (4,5) and it was higher in patients taking a combination of nasal and inhaled GC compared to those using nasal GC only (5). Fortunately, clinical symptoms of AI have been described only in a minority of these patients.

Drugs that inhibit cytochrome p450 (e.g. itraconazole, ritonavir and antidepressants) may interact with CG hepatic metabolism (via CYP3A4 isoenzyme) and lead to prolonged action of GC, therefore they should be considered during anamnesis (21).

Prescribing nasal glucocorticoids to pregnant women requires vigilance and CS during pregnancy requires a high index of suspicion because poor outcomes can occur in both mother and fetus if diagnosis is delayed (1,6). This is especially important because diagnosis can be overlooked given the fact that the syndrome can be easily confused with some other pathologies much more common in pregnancy such as preeclampsia (48) or gestational diabetes or even normal changes that occur in this physiologic state. In patients with a cushingoid appearance that contrasts with low levels of ACTH and cortisol, a detailed anamnesis should search for various types of glucocorticoid administration that can cause iatrogenic CS and secondary AI.

In conclusion, this case-report shows that even topical – intranasal – glucocorticoids spray may cause iatrogenic Cushing's syndrome and patients should be advised about the potential risk. During pregnancy, a special attention should be payed to pregnant women with chronic rhinitis/rhinosinusitis regarding the class of medications and the dosage recommended. Drug interactions should be taken into consideration, especially with agents that can inhibit cytochrome p450. Also, it needs to be emphasized that patients with iatrogenic Cushing's syndrome are at risk of having an adrenal crisis if they do not receive stress dose steroids during acute illness or even labor.

Conflict of interest

The authors declare that they have no conflict of interest.

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