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Cushing's syndrome diagnosed after delivery: a case report

Case Report

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Abstract: Introduction: During normal pregnancy there are significant changes in hypothalamic-pituitary-adrenal axis, with increased levels of plasma cortisol and adrenocorticotropic hormone which sometimes reach values observed in patients with Cushing's syndrome. Cushing's syndrome (CS) is rarely encountered during pregnancy, but is associated with serious maternal and fetal complications. Case presentation: A 31-year-old female was admitted to our institution four weeks after delivery. Physical examination revealed moon face, purple striae throughout the abdomen, bruising over the legs, a dorsocervical fat pad and hirsutism. She delivered a eutrophic preterm newborn at 34 weeks gestation, without any maternal or fetal complications during delivery. Imaging showed a mass in the right suprarenal gland with a normal pituitary. After four weeks the patient underwent a right adrenalectomy. The mass was eventually identified as an adrenocortical adenoma. Conclusion: In our case the diagnosis of CS was established only after pregnancy, which enabled the development of numerous adverse consequences secondary to increased plasma cortisol. If CS is recognized during pregnancy, treatment and its timing could be carefully chosen according to the patient's individual characteristics.

Keywords: *Cushing's Syndrome • Pregnancy • Delivery • Adrenalectomy.*

List of abbreviations

Cushing's syndrome (CS)
Adrenocorticotropic hormone (ACTH)
Corticotrophin - releasing hormone (CRH)
Hypothalamic - pituitary - adrenal (HPA) axis
Dexamethasone suppression test (DST)
Oral glucose tolerance test (OGTT)

1. Introduction

Cushing's syndrome (CS) encompasses a cluster of signs and symptoms caused by increased cortisol production in suprarenal gland. A rare disorder with an incidence of 2-3 cases per million, about 0.6 cases per million are caused by benign adrenal adenomas [1]. Making a diagnosis of CS is not straightforward since frequently not all signs, symptoms and laboratory abnormalities are present [2-5]. Untreated CS is associated with high morbidity and mortality [6]. Major metabolic consequences of increased cortisol are hyperglycemia, increased cellular glucogenesis and increased hepatic gluconeogenesis [7]. Due to increased protein catabolism and negative nitrogen balance, muscular atrophy, osteoporosis and fragility of connective tissue are often encountered. Levels of free fatty acids and cholesterol are increased in plasma, and a centripetal distribution of fatty tissue is characteristic [8-12].

Prolonged exposure to increased plasma glucocorticoids leads to a decrease in glomerular filtration, glomerular dysfunction and albuminuria [13]. Sodium and

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calcium are preserved, while potassium is increasingly excreted in urine. Fully developed CS causes significant disfiguration: a round, reddish and plethoric face, numerous pimples, a wide neck with fat pat at the base (buffalo hump), "barrel" thorax, prominent abdomen with violet striae on the skin, and easy bruising [14]. The extremities are relatively spared, and look thin in contrast to the trunk. This is frequently accompanied by hypertension, muscle weakness, disorders of menstrual cycle in women [15] and impotence in men. Increased glucocorticoids often cause changes in behavior (in 60%), depression and impairment of cognition [16,17]. Patients with CS have dysregulated coagulation and an increased risk of venous thrombosis [18-20].

CS in pregnancy is often associated with serious maternal and fetal complications: hypertension, preeclampsia, diabetes, spontaneous abortion, prematurity and stillbirth [21-23].

2. Case report

A 31-year-old female was admitted to our institution four weeks after her first delivery. She had no previous pregnancies. Her medical history was unremarkable and conception was spontaneous. She had pain in the lumbosacral spine from 10 weeks gestation, with only three episodes of about 3 weeks without pain. The intensity of pain varied from moderate to very severe, inhibiting normal movement. Spontaneous bruises on skin of the legs were present from the beginning of pregnancy. Physical examination revealed the following changes: moon face, purple striae throughout the abdomen, bruising over pressure areas, a dorsocervical fat pad and hirsutism. The patient's weight before pregnancy was 59 kg (body mass index 19.5kg/m^2) and weight gain during pregnancy was 12 kg (1 kg for the first 12 weeks, another 6 kg for the next 12 weeks, and 5 kg through the last 10 weeks of pregnancy). Systolic blood pressure during pregnancy and after delivery was between 115 and 125mmHg, with a diastolic of 80 mmHg. Morphology of the fetus at 20 weeks was unremarkable. The patient refused the first trimester combined test. Blood tests at 33 weeks,10 days before delivery, were within normal limits (white blood cells 5.3x10^9/L, red blood cells 3.99x10^{12}/l, platelets 212x10^9/l, Hb 134 g/L, glucose 4.3 mmol/L , urea 4.4mmol/L, creatinine 59 mmol/l, serum proteins 70 g/L, AST 23 U/l, ALT 19 U/L, cholesterol 3,80 mmol/L, LDL cholesterol 2,17 mmol/L, HDL cholesterol 1,13 mmol/L, triglycerides 1,10 mmol/L, Na^+ 143mmol/l, K^+ 4,4mmol/:, Cl^- 101 mmol/L, Ca^{2+} 2,4 mmol/L). Oral glucose tolerance test (OGTT) was not performed during pregnancy. At the same time, a routine urine test demonstrated an asymptomatic urinary tract infection (*Proteus mirabilis* was isolated) and oral cephalexin was prescribed (7 days, 1000 mg in two doses per day). She delivered a eutrophic preterm newborn at 34 weeks gestation (birthweight 2400 g, on the 33rd percentile of our population; Apgar score was 9 at 1 minute and 10 at 5 minutes , pH 7.30, pO_2 60 mmHG, pCO2 42 mmHg, HCO_3 18 mmol/L, oxygen saturations 82%), without any maternal or fetal complications during gestation, delivery or the postpartum period.

According to the clinical signs, hypercorticism was suspected by the physicians. A daily profile of cortisol, dexamethasone suppression test (DST), as well as plasma adrenocorticotropin hormone (ACTH) measurements were performed . The results of the biochemical screening were largely consistent with CS (Table 1).

Table 1. Results of pituitary and end organ hormone tests. ACTH - adrenocorticotropic hormone, TSH - thyroid-stimulating hormone, fT4 - free thyroxine.

Hormone	Results	Reference range (unit)
Serum cortizol (8 a.m.) (12 p.m.)	688 nmol/L 540 nmol/L	154-638 (nmol/L) 80 -388 (nmol/L)
ACTH	< 4.0 pg/ml	< 46.0 (pg/ml)
fT4	8.9 pg/ml	7-18 (pg/ml)
TSH	1.4 pg/ml	0.25-4.0 (mIU/L)

The daily serum cortisol variation was abnormal: the serum cortisol levels were 688 nmol/L at 08:00 (normal: 154 - 638 nmol/L) and 540 nmol/L at midnight (normal 80 - 388 nmol/L). The plasma ACTH was 4 pmol/L at 08:00 (normal: 9 - 46 pmol/L). Serum cortisol levels were not suppressed by 1mg of dexamethasone: the serum cortisol level was 620 nmol/L at 08:00 the following day. The results suggested mild hypercortisolism, with suppressed secretion of ACTH. OGTT showed normal glucose tolerance with compensatory hyperinsulinemia, as a consequence of the insulin resistance (glucose level at 0 minutes was 5.0 mmol/L, and at 120h minutes was 6.3 mmol/L). insulin levels were 33.5 µIU/mL and 188 µIU/ml at 0 and 120 minutes, respectively (reference range 4.3-19.9 µIU/mL) Clinically and biochemically the patient was euthyroid. Osteodensitometry showed osteoporosis (Z score: -3.5). Of the morphological examinations, an ultrasound (US) of adrenal glands showed an enlarged right suprarenal gland (2.8 cm x 2.9 cm), and an abdominal computerized tomography scan (CT) disclosed a right adrenal gland mass (3 x 2 cm) (Figure 1), while pituitary magnetic resonance imaging (MRI) scan was normal. According to the observed results of the examinations, a suprarenal gland adenoma was considered to be the most likely cause of primary hypercorticism.

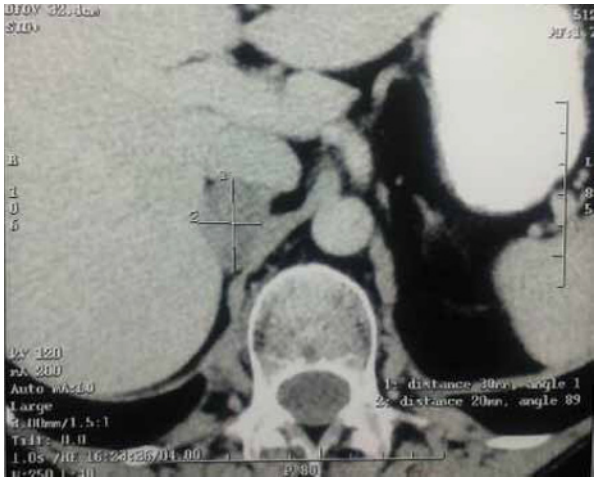

Figure 1.

The patient was prescribed ketoconazole (600 mg/day) and after four weeks she underwent a right surgical adrenalectomy by an open posterior approach. The mass was histologically identified as an adrenocortical adenoma (3 cm, weight 12 g). She was then prescribed 20 mg of hydrocortisone daily for a further 12 months. This therapy was subsequently discontinued when an ACTH test demonstrated adequate function of her hypothalamic - pituitary - adrenal (HPA) axis.

Every two months after delivery she was clinically and biochemically re-assessed. After twenty months from operation daily serum cortisol variations were normal.
The ACTH test (administration of 25 i.j. ACTH intravenously) was obtained 6 months after delivery and hydrocortisone (20 mg daily) was administered, without any response from the remaining suprarenal gland. The laboratory values of ACTH were increased for the next 12 months, as well as for the 12 months after cortisol serum level were normalized.

Repeated osteodensitometry after 12 months showed osteoporosis (Z score -2.7), and after 3 years the Z score was -1.4.

3. Discussion

During normal pregnancy there are significant changes in the hypothalamic-pituitary-adrenal axis, with increased levels of plasma cortisol and ACTH that sometimes reach values observed in patients with Cushing's syndrome. Probable causes of the increased levels of ACTH are its synthesis in the placenta, pituitary desensitization to cortisol and increased responsiveness of the pituitary to corticotropin-releasing hormone [24]. CS is rarely encountered during pregnancy and, up to 2007, there were fewer than 150 cases described in the medical literature [25]. The probability that a woman with CS will become pregnant is very small, because the increased plasma cortisol causes irregular menstruation and infertility [26]. If a pregnancy ensues, a benign adenoma of a suprarenal gland is far more frequent a finding than a pituitary tumor [27-29]. It is difficult to make a diagnosis of CS during pregnancy, since it shares some signs and symptoms with pre-eclampsia and gestational diabetes [30]. Physicians should consider CS in order to recognize its appearance during pregnancy. In this case, the diagnosis of CS was established only after pregnancy, which enabled the development of numerous adverse consequences of increased plasma cortisol: osteoporosis (which persisted for several years after pregnancy), moon face, purple striae throughout the abdomen, bruising over pressure areas, a dorsocervical fat pad and hirsutism. Serum cortisol levels exceeding 193 nmol/l at midnight in a non-stressed patients provide good specificity for the diagnosis of CS. The overnight 1 mg dexamethasone suppression test (DST) is a valuable screening test in patients with suspected hypercorticism. This study employes the adminstration of 1 mg of dexamethasone at bedtime (11:00 pm), with determination of a plasma cortisol early the following morning. Normal subjects should supress plasma cortisol to less than 50 nmol/L) following an overnight 1 mg test [2,5]. Owing to the fact that the increase in plasma cortisol was not severe, maternal and fetal outcomes were mostly good, and life-threatening complications did not develop during this pregnancy. However, Cushing's syndrome in pregnancy can be associated with severe maternal complications such as eclampsia, pulmonary oedema and fractures due to osteoporosis [31]. The most severe consequence of CS in our case was osteoporosis, which spontaneously improved over the course of 3 years.

If CS is recognized during pregnancy, treatment and its timing should be carefully chosen according to the patient's individual characteristics, in order to avoid maternal and fetal complications. Both an obstetrician and an endocrinologist should be involved in the treatment of such a patient. Maternal prognosis depends on the severity of hypertension, pre-eclampsia, diabetes and other complications. There are two therapeutic options for the pregnant patient with Cushing's syndrome – medical treatment and adrenalectomy. However, medical treatment turned out to be rather ineffective and potentially hazardous. When it comes to surgical treatment, recorded experience shows that operative intervention just after diagnosis is the most satisfactory [32,33].

Regarding the effect on fetal development, CS is associated with a higher rate of prematurity and fetal loss, as well as intrauterine growth restriction, but serious

perinatal complications were not described in former recorded cases [32,]. If an adrenocortical carcinoma is the cause of Cushing's syndrome, fetal prognosis is no different than in cases when Cushing's syndrome is due to an adrenocortical adenoma [34,35]. Early treatment improves prognosis, and its delay could be deleterious [36].

Consent

Written informed consent was obtained from our patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MA, VM and SJ have made substantial contributions to the analysis and interpretation of the patient data and were a major contributors in writing the manuscript. VM and AD performed the endocrinological examination and have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and have given approval of the final version of the manuscript to be published.

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References

[1] Steffensen C., Bak A.M., Rubeck K.Z., Jorgensen J.O., Epidemiology of Cushing's syndrome, Neuroendocrinology, 2010, 92 Suppl 1:1-5

[2] Alves M., Neves C., Medina J.L., Laboratorial diagnosis of Cushing's syndrome, Acta Med Port., 2010, 23(1),63-67

[3] Aron D.C., Cushing's syndrome: why is diagnosis so difficult? Rev. Endocr. Metab. Disord. 2010, 11(2):105-116

[4] Vilar .L, Freitas Mda .C., Faria M., Montenegro R., Casulari L.A., Naves L., Bruno O.D., Pitfalls in the diagnosis of Cushing's syndrome, Arq. Bras. Endocrino.l Metabol., 2007, 51(8),1207-1216

[5] Santos S., Santos E., Gaztambide S., Salvador J., Diagnosis and differential diagnosis of Cushing's syndrome, Endocrinol. Nutr., 2009, 56(2),71-84

[6] Bolland M.J., Holdaway I.M., Berkeley J.E., Lim S., Dransfield W.J., Conaglen J.V., et al., Mortality and Morbidity in Cushing's syndrome in New Zeland, Clin. Endocrinol. (Oxf.), 2011, May 24.doi 10.1111/j.1365-2265.,2011,014124

[7] Chanson P., Salenave S., Metabolic syndrome in Cushing's syndrome. Neuroendocrinology., 2010, 92 Suppl 1:96-101

[8] Szappanos A., Toke J., Lippai D., Patocs A., Szucs N., Futo L., et al., Bone turnover in patients with endogenous Cushing's syndrome before and after succesful treatment., Osteoporos. Int., 2010, 21(4):637-645

[9] Bednarek-Tupikowska G., Kubicka E., Hypercortisolism in pregnancy, Pol. Merkur Lekarski. 2006, 20(116),232-235

[10] Peris P., Guanabens N., Martinez de Osaba M.J., Monegal A., Alvarez L., Pons F., et al., Clinical characteristics and etiologic factors of premenopausal osteoporosis in a group of Spanish women, Semin. Arthritis. Rheum. 2002, 32(1),64-70

[11] Randazzo M.E., Grossrubatscher E., Dalino Ciaramella P., Vanzulli A., Lili P., Spontaneous recovery of bone mass after cure of endogenous hypercortisolism, Pituitary, 2011 Apr 8. DOI: 10.1007/s11102-011-0306-3

[12] Takeshita M., Mizuno Y., Effect of glucose and bone metabolism in endocrinal disorder, Clin. Calcium., 2009, 19(9),1282-1290

[13] Smets P., Meyer E., Maddens B., Daminet S., Cushing's syndrome, glucocorticoids and the kidney, Gen. Comp. Endocrinol., 2010, 169(1),1-10.,

[14] Bruno O.D., Juarez-Allen L., Rossi M.A., Longobardi V., In what clinical settings should Cushing's syndrome be suspected?, Medicina (B. Aires). 2009, 69(6),674-680

[15] Kalantaridou S.N., Makrigiannakis A., Zoumakis E., Chrousos G.P., Stress and female reproductive system, J. Reprod. Immunol., 2004, 62(1-2),61-68

[16] Sonino N., Fallo F., Fava G.A., Psychosomatic aspects of Cushing's syndrome, Rev. Endocr. Metab. disord., 2010, 11(2),95-104

[17] Wolkowitz O.M., Burke H., Epel E.S., Reus V.I., Glucocorticoids. Mood, memory, and mechanisms, Ann. N Y Acad .Sci., 2009, 1179,19-40

[18] Manetti L., Bogazzi F., Giovannetti C., Raffaelli V., Genovesi M., Pellegrini G., et al., Changes in coagulation indexes and occurence of venous thromboembolism in patients with Cushing's syndrome: result from a prospective study before and after surgery, Eur. J. Endocrinol., 2010, 163(5),783-1891

[19] Van Zaane B., Nur E., Sqizzato A., Dekkers O.M., Twickler M.T., Fliers E., et al., Hypercoagulable state in Cushing's syndrome: a systematic review, J. Clin. Endocrinol. Metab., 2009, 94(8),2743-2750

[20] Erem C., Nuhoglu I., Yilmaz M., Kocak M., Demirel A., Ucuncu O., et al., Blood coagulation and fibrinolysis in patient with Cushing's syndrome: increased plasminogen activator inhibitor-1, decreased tissue factor pathway inhibitor, and unchanged thrombin-activatable fibrinolysis inhibitor levels, J. Endocrinol. Invest., 2009,32(2),169-1674

[21] Kita M., Sakalidou M., Saratzis A., Ioannis S., Avramidis A., Cushing's syndrome in pregnancy: report of a case and review of the literature, Hormones (Athens), 2007, 6(3),242-246

[22] Bertherat J., Bilaud L., Guilhaume B., Cushing's syndrome and adrenal insuffiency in pregnancy, Ann. Endocrinol. (Paris), 2002, Oct,63(5),452-456

[23] Delibasi T., Ustun I., Aydin Y., Berker D., Erol H.K., Gul K., et al., Early severe pre-eclamptic findings in a patient with Cushing's syndrome. Gynecol. Endocrinol., 2006, 22(12),710-712

[24] Lindsay J.R., Nieman L.K., The hypotalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment, Endoc. Rev., 2005, 26(6),775-799

[25] Vilar L., Freitas Mda C., Lima L.H., Lyra R., Kater C.E., Cushing's syndrome in pregnancy: an overview, Arq. Bras. Endocrinol. Metabol., 2007, 51(8),1293-1302

[26] Bednarek-Tupikowska G., Kubicka E., Hypercortisolism in pregnancy, Pol. Merkur Lekarski, 2006, 20(116),232-235

[27] Pollack R.P., Brett E.M., Adrenocorticotropic hormone-independent Cushing's syndrome manifesting during pregnancy, Endocr. Pract., 2010, 16(2),260-263

[28] Terhune K.P., Jagasia S., Blevins L.S.Jr., Phay J.E., Diagnostic and therapeutic dilemmas of hypercortisolemia during pregnancy: a case report. Am. surg., 2009, 75(3),232-4,

[29] Lo C.Y., Lo C.M., Lam K.Y., Cushing's syndrome secondary to adrenal adenoma during pregnancy, Surg Endosc., 2002,16(1),219-220

[30] Kim Hg, Lee K.H., Je G.H., Han M.S., A case of Cushing's syndrome in pregnancy secondary to an adrenal cortical adenoma, J. Korean Med. Sci., 2003, 18(3),444-446

[31] Choi WJ, Jung TS, Paik WY. Cushing's syndrome in pregnancy with a severe maternal complication: a case report. J Obstet Gynaecol Res. 2011,Feb;37(2):163-167

[32] Sammour RN, Saiegh L, Matter I, Gonen R, Shechner C, Cohen M, Ohel G [Dickstein G. Adrenalectomy for adrenocortical adenoma causing Cushing's syndrome in pregnancy: a case report and review of literature. Eur J Obstet Gynecol Reprod Biol. 2012 Jun 13. [Epub ahead of print] PubMed PMID: 22698457

[33] Holgado-Galicia MV, Magno JD, Acelajado-Valdenor C, Isip-Tan IT, Lim-Abrahan MA. Cushing's syndrome in pregnancy. BMJ Case Rep. 2011 Apr 26;2011. pii: bcr0120113720. doi: 10.1136/bcr.01.2011.3720. PubMed PMID: 22696666

[34] Homer L, Viatge M, Gayet FX, Laurent Y, Kerlan V. [Cushing syndrome and pregnancy: a propos of a malignant adrenocortical carcinoma]. Gynecol Obstet Fertil. 2012 Mar;40(3):e1-4

[35] Kotteas E, Ioachim E, Pavlidis N. A pregnant patient with adrenocortical carcinoma: case report. Onkologie. 2012;35(9):517-951

[36] Lubin V, Gautier JF, Antoine JM, Beressi JP, Vexiau P. Cushing's syndrome during pregnancy. Presse Med. 2002; 31(36):1706-1713