Case Report

Journal of Emergency Medicine Case Reports

A Report of Recurring Pregnancy-İnduced Cushing's Syndrome

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Abstract

Introduction: The incidence of pregnancy-induced Cushing's syndrome (CS) is very low. However, the diagnosis of CS in pregnant patients is very difficult because of an overlapping signs and symptoms.

Case report: Herein, a 20-year-old pregnant patient was reported that was afflicted by gestational CS during two pregnancies; termination of pregnancy was carried out in both cases. Bilateral adrenal hypertrophy was reported in magnetic resonance imaging. Following therapeutic abortion, signs of chemical evidence of CS was thoroughly regressed within a few months after each abortion without any treatment.

Conclusion: Due to the temporal relation between the occurrence of CS after each pregnancy the diagnosis of gestational hypercortisolism was made, and for further pregnancies bilateral adrenalectomy was recommended.

Key Words: Cushing`s syndrome, pregnancy, adrenal hypertrophy

Introduction

The functional physiology of several systems differs in pregnancy secondary to both fetal and maternal causes. The endocrine system is also affected by pregnancy-induced homeostasis among all other systems. Due to the associated infertility and inhibition of gonadotropin secretion, Cushing`s syndrome (CS) is rarely reported in a pregnant woman[1]. Moreover, aberrant expression of receptors of luteinizing hormone (LH) and human chorionic gonadotropin (HCG) in the adrenal membrane further decrease the likelihood of primary hypercortisolism syndrome in pregnancy. Regardless, development of CS during pregnancy poses serious threats to both the pregnant mother and the embryo, such as premature delivery and stillbirth[2, 3]. In the current study, we report the occurrence of CS in a young woman during two consecutive pregnancies that both developed during the first trimester of pregnancy. In both occasions, CS was fully remitted following termination of pregnancy without any further therapy.

Case Report

A 20-year-old woman with polycystic ovarian syndrome (PCOS) was successfully treated with clomiphene for infertility and pregnant in September of 2016 for the first time. She experienced out of proportion abdominal obesity, excessive striosis, exacerbation of hirsutism (Grade 20 on Ferriman-Gallwey scale)[4], increased facial hair and myasthenia during the first trimester of her pregnancy. Initial diagnosis of ovarian hyperstimulation syndrome (OHSS) was made and due to concomitant intrauterine growth retardation (IUGR), the pregnancy was electively terminated at the 8th week. All associated symptoms spontaneously regressed within 2-3 months after the abortion. The second pregnancy was induced with a pulse treatment of letrozole 5 mg, followed by 3 every other day injections of 100 units recombinant follicle-stimulating hormone (rFSH) in November 2017. Within the first 4 weeks into the second pregnancy, the patient developed recurrence of OHSS symptoms (Figure 1). In addition to the prior symptoms and progressive proximal myasthenia, the patient developed hypertension, round moon-like face, back hump, and suprasternal fat pad consistent with the typical features of CS.

In week 14 of pregnancy, the patient complained from acute-onset bilateral blindness and hypertension (blood pressure of 180/120 mmHg), which soon progressed into loss of consciousness and grand-mal seizure. She was admitted to the intensive care unit (ICU) with a preliminary diagnosis of intracerebral bleeding. Magnetic resonance imaging (MRI) of the brain was performed which ruled out intracerebral/pituitary hemorrhages/lesions. Admission laboratory testing

Corresponding Author: Mitra Niafar **e-mail:** dr.mniafar@gmail.com
Received: 16.10.2019 • **Accepted:** 17.01.2020
DOI:10.33706/jemcr.633840

DOI:10.33706/jemcr.633840
Journal of Emergency Medicine Case Reports 2020; 11 (1):13-16

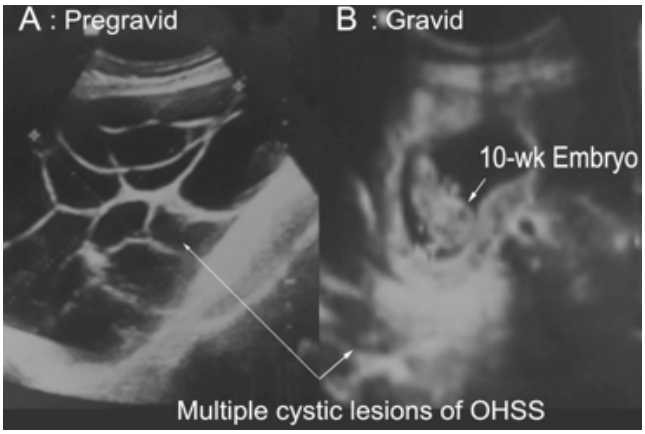

Figure 1. Abdominal ultrasound of the pelvis before the conception (A), showing a large ovary containing multiple cysts (OHSS) and (B) a normal intrauterine pregnancy.

included those to assess the function of the pituitary-adrenal axis (HPA) due to the presence of symptoms related to CS. This test battery included determination of serum concentrations of baseline cortisol and after low-dose dexamethasone suppression, serum adrenocorticotropic hormone (ACTH), renin, aldosterone, and 24-hour urine concentrations of free cortisol, normetanephrine and metanephrine. Additional laboratory findings upon admission included progressive increases in aspartate aminotransferase (AST; 119 → 522 U/L); alanine aminotransferase (ALT; 191→ 368 U/L) and borderline platelet count. Based on available clinical information a diagnosis of hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome was made and emergency termination of pregnancy was carried out at the gestational age of 14 weeks.

The patient`s clinical signs such as hypertension and acute blindness were totally subsided soon after the therapeutic abortion. An additional endocrinological investigation was obtained during the postoperative period while the patient was still hospitalized. Diagnosis of ACTH independent CS was made based on elevated 8 a.m. serum cortisol level unresponsive to low-dose dexamethasone (45→41 µg/dL), elevated urine cortisol, lower ACTH and normal level of serum renin, aldosterone and urine concentrations of metanephrine and normetanephrine. The patient was discharged from the hospital after she recovered from the acute blindness, normalization of the blood pressure and declining liver enzymes.

She was then followed up as an outpatient with the University Endocrine Center. With an exception of myasthenic symptoms, all other symptoms fully recovered within a 2-3 month period. The results of muscular examination of the patient revealed proximal (3 out of 5) and distal (4 out of 5) myasthenia and at the bedside, the patient was not able to get down the bed easily and walk without help. Serial values reveal a gradual decrease in beta- HCG along with serum and

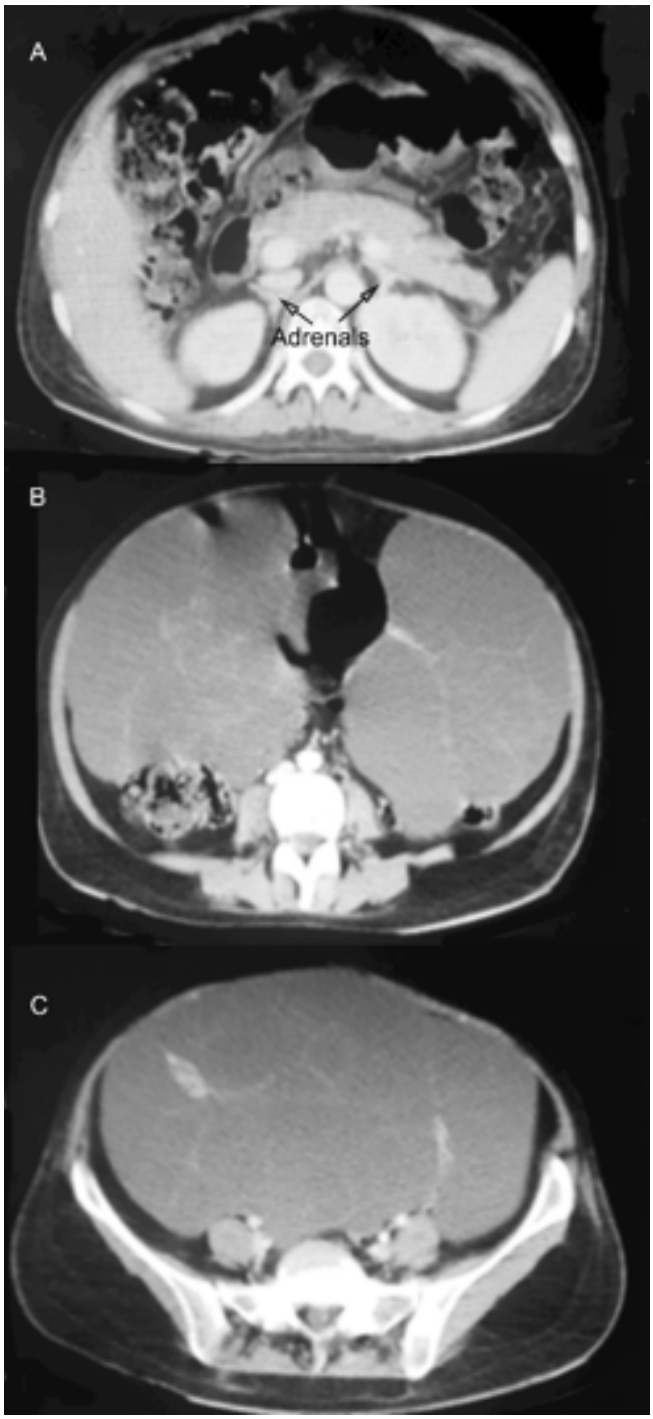

Figure 2. Computer tomographic scan of the adrenal glands showing enlarged adrenals (A), and huge ovaries containing multiple cysts (B and C).

urine cortisol concentrations, which paralleled with gradual increases in ACTH levels (Table 1). The results of CT scan of abdomen and pelvis requested for the patient during the previous hospitalization revealed bilateral hypertrophy of adrenal glands (Figure 2A) in addition to massive bilateral pelvic mass (Figure 2B and 2C). An ultrasound study of the pelvis revealed bilateral polycystic deformation of both ovaries containing multiple parietal nodules. The borderline values ovarian biomarkers, i.e., alpha-1-fetoprotein (AFP)

Table 1. Laboratory findings.

Parameters	Abortion	After abortion							
Date	3/7/18	4/5/18	4/9/18	4/28/18	5/7/18	5/15/18	6/1/18	7/28/18	11/22/18
Beta-HCG (mIU/mL)	838	258	201	100	-	57.6	28.5	16	-
Serum Cortisol (µg/dL)	45	-	-	-	19.1	-	-	6.7	17.7
24 h Urine Free Cortisol (µg/day)	1984	-	346	70	-	-	71.4	-	-
Adrenocorticotropic hormone (pg/ml)	3	-	<5	-	<5	-	-	21.2	16.9

of 4 ng/L, carcinoembryonic antigen (CEA) of 7.1 ng/mL and cancer antigen (CA125) of 151 U/mL were compatible with PCOS. Additionally, serum testosterone concentration was 3.4 nmol/L which later decreased to 0.64 nmol/L without further treatment, and other androgen levels also remained at their borderline levels (dehydroepiandrosterone sulfate DEHAS = 1.27 µmol/L; 17 hydroxyprogesterone (17-OHPG) of 1.86 ng/mL.

Discussion

Cushing`s syndrome rarely occurs during pregnancy[1]. Diagnosis of CS in pregnancy is challenging as the physiological changes during pregnancy may mimic those of CS. Moreover, the placental production of corticotropin releasing hormone (CRH) may result in some symptoms of CS by stimulating the ACTH/cortisol axis. In fact, both free and protein-bound concentrations of cortisol in plasma and urine significantly increase during a normal gestation. Dexamethasone suppression dose generally fails to reduce cortisol levels to the extent that is seen in a non-pregnant individual. Both maternal and fetal complications such as growth retardation, premature birth and stillbirth occur more frequently in the presence of CS[5]. But in our case, postpartum remission of CS after the two consecutive pregnancies suggests a temporal cause-effect relationship between CS and gravidity.

The choice of a treatment strategy for gestational CS is very complex and it varies from one case to another. Among the factors that determine the choice of therapy, maternal age and the severity of disease are very important. The use of metyrapone and/or ketoconazole for treatment of gestational CS have been used with a great success in patients with high operative risk and also for the preparation of patients for surgical treatment[6].

In a study performed by Bevan et al., a woman was diagnosed with CS during the 29th gestational week. Following a course of metyrapone and adrenalectomy in week 31, the patient underwent a successful vaginal delivery in week 36 of pregnancy[7]. Long-term treatment of gestational CS has not been as successful. However, in the case of adrenal hyperplasia, bilateral adrenalectomy offers a certain cure. Abbassy et al. reported that bilateral adrenalectomy effectively treated a 38-year-old patient who was diagnosed with gestational CS[2]. In another report, a 26-year-old patient with a diagnosis of non-ACTH dependent CS during week 19 of pregnancy underwent laparoscopic adrenalectomy with a very good outcome[8]. Although adrenalectomy is now considered the only cure for gestational CS, its timing during pregnancy is still a matter of debate. However, most surgeons prefer to perform adrenalectomy at the second trimester of pregnancy[9]. Our patient had a therapeutic abortion due to severe maternal complications and development of CS during the early gestational age. The patient was reeducated on the subject of contraception and the possibility of adrenalectomy for future pregnancies.

The case report has written in an anonymous characteristic, thus secret and detailed data about the patient has removed. Editor and reviewers can know and see these detailed data. These data are backed up by editor and by reviewers.

Conclusion

In conclusion, we present a patient with reversible pregnancy-induced Cushing Syndrome that led to untimely termination of pregnancy. As expected, serum cortisol levels returned to normal levels during one month, and the clinical manifestations of Cushing completely disappeared in 90 days. It is perceived that the symptoms of Cushing syndrome secondarily developed to an unusual presence of ectopic adrenal LH/hCG receptors that release cortisol in response to hCG stimulation. A proper diagnosis perhaps offers more options such as adrenalectomy to the patients who wish to have children. Adrenalectomy also provides needed tissue samples for immunohistochemistry staining which confirms the expression of LH/hCG receptors by the ectopic adrenal cells.

Conflict of interests

Authors declare no conflict of interests.

DOI:10.33706/jemcr.633840
Journal of Emergency Medicine Case Reports 2020; 11 (1):13-16

Financial Disclosure

The authors declared that this study has received no financial support.

Acknowledgment

Authors would like to acknowledge Dr. Nader Nader Djalal at Department of Anesthesiology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14203, USA for his great help.

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