

Cushing's Syndrome Complicating Pregnancy

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Abstract

To reveal Cushing's syndrome in pregnancy is difficult since there are no worldwide consent guidelines for making a definitive diagnosis. Some advocate using urine free cortisol as more than four times the upper limit of normal or salivary cortisol is two to three times above. It is also difficult to evaluate the optimal time of surgical intervention because most cases are diagnosed at or beyond their second trimester. In the case describe below, the disease was being suspected because there was a lost circadian variation of serum cortisol, which could be a reasonable initiate test for clinical suspicious cases in our further practice.

Keywords: Cushing's syndrome; Pregnancy; Urine; Ultrasound

Case Report

A 28-year-old pregnant woman who is free of past medical history was being referred to medical out-patient-department at gestational age 15 weeks with the complain of sensation of generalized distention over face, neck, hands and both lower limbs since Nov 2014. She enjoyed good past health and that was her first time of perception. The thyroid function test at that time revealed mildly lowered total T3, FT3 but normal FT4 and TSH levels and mildly increased morning cortisol level at 21.7 µg/dL (6.19 µg/dL to 19.43 µg/dL in nonpregnant women) during medical work up. To repeat her FT4 and TSH on 7 Aug 2015 revealed levels within normal range but the increased morning cortisol level remained at 20.04 µg/dL. The physical examination during her consultation showed no appreciable Cushingoid appearance i.e. moon faces, buffalo hump, truncal obesity, supraclavicular fat pads and her blood pressure was normal.

Since pregnancy can normally cause hypercortisolism and Cushing's syndrome/disease associated pregnancy is extremely rare, morning and afternoon serum cortisol were tested in an attempt to rule out pathological condition. Beyond expectation, the results showed loss of circadian variation. Two times of low dose (1 mg) dexamethasone suppression test was performed showing no suppression of serum cortisol. ACTH independent Cushing syndrome was considered when an elevated serum cortisol was correspond to a suppressed ACTH level (Table 1). A morphology ultrasound was performed on 2 Oct 2015 (GA 23+w) showing normal fetal growth and development. Adrenal USG performed on the same day failed to demonstrate adrenal abnormalities. The woman was diagnosed ACTH independent Cushing's syndrome base on a suppressed plasma ACTH together with non-suppression on low dose dexamethasone suppression test. Subsequent non-contrast MRI showed a 3.5 cm left side adrenal tumor. Removal of the tumor by laparoscopic surgery was performed on 14 Oct 2015, pathology of which suggested adrenal cortical adenoma (Figure 1).

After resection of adenoma, the patient recovered well, given replacement of hydrocortisone 20 mg am and 10 mg pm with close monitor of blood pressure and serum glucose level. A baby boy weight 2.86 kg was given birth by vaginal delivery on 1st Jan 2016 at GW 36w6d with full Apgar score in Macau. She is subsequently discharged with hydrocortisone replacement (Table 1).

Discussion

Cushing syndrome occurs only rarely in pregnant women because hypercortisolism results in ovulatory disturbances and relative infertility. So far, with fewer than 150 cases of Cushing syndrome in pregnancy have been reported in the literature. When Cushing syndrome occurs

during pregnancy, it may be difficult to detect clinically because of the central weight gain, abdominal striae, increased blood pressure, and glucose intolerance associated with normal pregnancy [1-8]. Pregnancy dramatically affects the hypothalomo-pituitary-adrenal (HPA) axis and the endogenous secretion of cortisol, with total and free serum cortisol concentrations reaching levels higher than those compared to non-pregnant controls. The placenta produces corticotrophin-releasing hormone (CRH) and ACTH. ACTH values cannot be relied upon to distinguish ACTH-independent from ACTH-dependent forms of CS in pregnancy. Both low- and high-dose overnight dexamethasone suppression tests do not yield accurate results because dexamethasone may increase placental CRH and placental ACTH activity [1,2,9].

Laboratory confirmation of the diagnosis in pregnancy is not well established due to the lack of reference ranges for the usual interpretive tests in women who are pregnant. However, the normal circadian rhythm of plasma cortisol is preserved in a healthy pregnant person, and, because this is often lost in patients with Cushing syndrome, it could be used as a useful preliminary test [1,2].

Approximately 60% of hypercortisolemia in pregnancy is caused primarily by adrenal adenomas, with pituitary adenoma accounting for 15% and adrenal carcinoma for 9% [1,9]. Cushing's syndrome in pregnancy has been associated with increased maternal morbidity, including gestational diabetes mellitus, hypertension, pre-eclampsia and maternal death [9]. It is this increased rate of maternal and perinatal morbidity and mortality that prompted interventional attempts to improve outcome in pregnancies complicated by Cushing's syndrome [9]. Medical treatment with metyrapone, ketoconazole and cyproheptadine was reported to be successful in a few cases. In many others, however, it has been shown to be ineffective and potentially hazardous. Surgery, on the other hand, has been more uniformly reported to be successful and was recommended by many authors as a first choice [1,2,6,10-13]. Historically, the optimal time for surgical intervention during pregnancy was the second trimester. At that time, the risk for spontaneous miscarriages is significantly reduced compared with the first trimester, yet the uterus is not large enough to impede intra-abdominal procedures. Indeed, most authors who have performed

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Received December 03, 2016; Accepted January 10, 2017; Published January 16, 2017

Citation: Hung IK, Hou N, Wa TK (2017) Cushing's Syndrome Complicating Pregnancy. J Clin Case Rep 7: 911. doi: 10.4172/2165-7920.1000911

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Date d/m/y	Morning serum cortisol (6.19 to 19.43) µg/dl in non-pregnant	Afternoon serum cortisol at 16:00H (2.68 to 10.50) µg/dl in non-pregnant	1 mg dexam suppression test (<1.8 µg/dl)	ACTH (10 to 46) pg/ml
4/3/2015 (before pregnant)	20.17 µg/dl			
7/8/2015 (GW 15+w)	20.04 µg/dl			
28/8/2015 (GW 18+w)	25.55 µg/dl	24.47 µg/dl		
11/9/2015 (GW 20+w)			29.47 µg/dl	
18/9/2015 (GW 21+w)			27.93 µg/dl	
17/9/2015	27.20 µg/dl			<5 pg/ml

Table 1: Summary of serial serum cortisol level, low dose dexamethasone suppression test and ACTH during work up.



Figure 1: Non-contrast MRI showing 3.5 cm left adrenal tumor.

adrenalectomy during pregnancy have advocated intervention in the second trimester. However, a policy of postponing surgical procedures until 31-32 weeks, when fetal lung maturity is significantly improved and preterm delivery is less critical, seems reasonable as well [2,9].

Conclusion

Cushing syndrome occurs only rarely in pregnant women because hypercortisolism results in ovulatory disturbances and relative infertility. Pregnancy affects the HPA axis by increasing endogenous secretion of

cortisol, together with the placenta production of CRH and ACTH, distort the interpretation of all the laboratory parameters, and hence making the diagnosis a conundrum [2,9,10]. Furthermore, the rarity of the disease and thus lack of statistic data preclude establishment of laboratory diagnostic criteria. However, the normal circadian rhythm of plasma cortisol is preserved in a healthy pregnant woman, it could be used as an useful preliminary test.

In this case, the loss of circadian variation in the preliminary work up raised the suspicion of the disease, and the markedly suppressed ACTH led to the diagnosis of ACTH-independent Cushing syndrome. The mainstay of treatment is surgical intervention, which was reported to be successful in terms of reduction in perinatal mortality and maternal morbidity rates. The optimal time for surgical intervention during pregnancy was the second trimester due to the benefit mentioned above. In our case, laparoscopic surgery was performed at GA 25+w. Optimal postoperative steroid replacement ensured a vaginal delivery to a healthy baby.

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