UNCOMPLICATED PREGNANCY IN A PATIENT WITH CUSHING'S DISEASE

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The coexistence of Cushing's syndrome (CS) and pregnancy is uncommon due to the suppression of gonadotropin secretion in CS. Adrenocorticotrophic hormone (ACTH) dependent CS in pregnancy is less frequent than adrenal causes. The diagnosis of CS during pregnancy is difficult since physiological changes in the hypothalamo-pituitary-adrenal axis may cause dynamic tests to be misinterpreted. Radiological imaging is limited.

We report the case of a 27-year old woman with Cushing's disease (CD) diagnosed in the 5th-week of pregnancy. The mild symptoms of hypercortisolism did not lead to serious complications for the mother or the fetus, so insulin was the only treatment used. The pregnancy was completed without any complications, and at 38 weeks of gestation a healthy female infant was delivered vaginally. Complications, such as hypocortisolemia and hypoglycemia, were not observed in the infant. Postpartum tests were consistent with CD. Contrast-enhanced pituitary magnetic resonance imaging revealed a microadenoma which was removed with transsphenoidal surgery. Histopathology revealed a pituitary adenoma with positive immunohistochemical staining for ACTH. Biochemical remission required prednisolone treatment, but the insulin requirement decreased significantly over time. As a conclusion, CD with mild features can be well tolerated during pregnancy, but the mother and the fetus must be monitored closely.

Key words: Pregnancy, Cushing's disease, hypercortisolemia, conservative treatment.

INTRODUCTION

The coexistence of Cushing's syndrome (CS) and pregnancy is rare, since hyperandrogenism and hypercortisolism inhibit gonadotropin secretion (1-4). Cushing's disease (CD), less common than adrenal CS, is rarely reported as a case presentation (2, 5-14). It is possible that patients with CD are less ovulatory than those with adrenal CS, perhaps because they are more hyperandrogenic (3, 15). Furthermore, cyclical CD due

to an adrenocorticotrophic hormone (ACTH) producing pituitary adenoma with fluctuating ACTH levels was also reported during pregnancy (16).

It is difficult to detect CS in pregnancy, because weight gain, slight hirsutism, acne, striae, hypertension and glucose intolerance in pregnancy are also components of CS. However, the laboratory evaluation of CS during pregnancy is complicated because of the increased activity of hypothalamic-pituitary-adrenal (HPA) axis in normal pregnancies (3, 4, 17, 18) and also there are no data as to how the certain diagnostic criteria should be modified to allow for the pregnancy-induced hypercortisolism. In addition to these, radiological examination is also limited.

Hypercortisolemia caused CS in pregnancy leads to serious complications for the mother and the fetus, and it is associated with prematurity and high fetal mortality (1, 3, 14, 19). Therefore, early diagnosis and treatment is crucial. The choice of treatment, either medical or surgical, depends on the severity of the disease and time of gestation. Conservative management without specific treatment is also convenient for some cases.

We report here a rare case of a pregnant woman with CD, the course of the disease until delivery and review of the literature.

CASE REPORT

A 27-yr-old Turkish female investigated in the gynecology clinic for recurrent pregnancy loss was referred to our endocrinology clinic for recently diagnosed diabetes mellitus (DM). She had a nine-month history of weight gain, menstrual irregularity and hirsutism. On physical examination she had facial plethora, mild increased dorsocervical fat, facial hirsutism, supraclavicular fullness, purple abdominal striae and normal blood pressure. On admission she had DM (blood glucose level of 13.4 mmol/L with an

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HbA1c value of 8.1 %), the glycated hemoglobin level suggesting that DM may have pre-dated conception. NPH insulin and metformin treatment was started. On her next visit, she reported a confirmed pregnancy at 5 weeks gestation and chose to complete her pregnancy. Further work-up revealed an elevated urinary free cortisol (UFC) “5-times the normal range” and midnight salivary cortisol and unsuppressed 1mg-overnight dexamethasone suppression test, which were consistent with CS (Table 1). No adrenal lesion was detected by ultrasound imaging. Non-contrast pituitary magnetic resonance imaging (MRI) in the second trimester visualized an asymmetric pituitary gland with suspect lesion in the right side without discrete mass (Fig. 1). She did not have severe clinical features of hypercortisolemia but mild cushingoid features with new onset DM. No signs of hyperlipidemia or hypertension were present so she was only treated with insulin (NPH and regular). During follow up, insulin requirements remained higher (1.5-2 U/kg daily) than expected for gestational DM, but her blood glucose was kept within range 4.2-7.8 mmol/L. Ultrasound

imaging showed normal fetal growth and anatomy with no signs of macrosomia, polyhydramnios or intrauterine growth retardation (IUGR). Monitored weekly by the endocrinology and obstetrics clinics, she delivered a healthy female infant weighing 2700-gr at 38 weeks of gestation with no signs of hypoglycemia or adrenal insufficiency. Peri/postpartum infections or preeclampsia did not occur.

Three months postpartum, the patient still had mild cushingoid features on physical examination. Plasma cortisol levels were not suppressed with 1 mg-overnight ($>1.8 \mu\text{g/dL}$) and low dose dexamethasone suppression test (LDST). High dose dexamethasone (HDST) suppressed cortisol levels ($>50\%$ suppression from baseline serum cortisol) and ACTH level was close to the upper normal range (Table 1). Contrast-enhanced pituitary MRI revealed a 7-mm adenoma on the right side of the pituitary (Fig. 2) and there was no adenoma or significant hyperplasia in adrenal glands by ultrasound imaging. Transsphenoidal adenomectomy was performed with 200 mg hydrocortisone infusion. Histopathology revealed a pituitary adenoma with

Table 1. Results of biochemical testing during pregnancy and postpartum

	Cortisol (08.00 h) $\mu\text{g/dL}$ (5-25)*	Midnight salivary cortisol (24.00 h) $\mu\text{g/dL}$ (<0.1) ^a	UFC $\mu\text{g/24h}$ (36-137)*	ACTH pg/mL (0-46)*	Overnight 1mg- DST	LDST	HDST
At presentation	26.7	0.7	691	75	20.9	ND	ND
At 3 months postpartum	22.3	ND	ND	38	12.3	17.5	4.6

^aCut-off midnight salivary cortisol; * Normal range; UFC (urinary free cortisol); DST (dexamethasone suppression test); LDST (low dose dexamethasone suppression test; 2mg 48-h); HDST (high dose dexamethasone suppression test; overnight 8 mg); ND, not done.

Figure 1. Coronal T1-weighted non-contrast MR scan (during second trimester) demonstrates asymmetry of the pituitary gland with the right side of the gland more prominent than the left (arrows). No discrete mass is seen.

Figure 2. Coronal contrast-enhanced T1-weighted MR scan identifies a 7x5 mm adenoma (arrows) in the right side of the pituitary (postpartum).

positive immunohistochemical staining for ACTH. Biochemical remission (postoperative early cortisol level was 0.4 µg/dL) required prednisolone treatment (5mg/dL), but the insulin requirement decreased significantly over time. HPA recovered about sixteen months and prednisolone treatment was stopped. Plasma cortisol level was suppressed with 1mg -overnight dexamethasone suppression test (cortisol level was 0.8 µg/dL). When last seen at outpatient clinic almost 38 months postoperatively, she was in remission and her blood glucose was controlled only by medical nutrition therapy. Her child was healthy.

DISCUSSION

Placental corticotropin-releasing hormone (CRH) and increased corticosteroid-binding protein are responsible for the transient and physiological hypercortisolism in pregnancy. Therefore, plasma cortisol, UFC and ACTH levels increase but the pulsatile and circadian rhythm of cortisol usually remains intact during normal pregnancy (3, 4, 17, 18, 20, 21). The increase in UFC starts at the 11th week of gestation. It continues to rise in the second trimester and is plateaued in the third trimester (22). ACTH levels increase almost 3-fold from the end of the first to the third trimester of pregnancy (23). For these reasons, it is difficult to diagnose CS with mild cushingoid features in pregnant women particularly in the second and third trimesters. Endocrine Society Clinical Practice Guideline recommends the initial use of one test with high diagnostic accuracy (UFC, midnight salivary cortisol, 1 mg overnight or LDST, HDST) in CS (24). As for diagnostic tests in pregnancy, midnight cortisol levels increase, but there is no diagnostic threshold for midnight plasma or salivary cortisol and LDST is blunted in pregnant women (18, 25). Therefore, UFC is the recommended screening test for CS during pregnancy. Above the normal range in the first trimester or a 3-fold increase in the second and third trimesters are significant for diagnosis (3). In our patient, UFC was 5-times the normal range and ACTH level was above the normal range although the patient was in the first trimester.

If CS is highly suspected or confirmed, the next step should be to determine the etiology. Generally, ACTH is helpful for differential diagnosis. Suppressed levels of ACTH suggest an adrenal etiology in CS during pregnancy. But detectable ACTH levels do not exclude adrenal etiology, since ACTH levels increase during the normal course of pregnancy (21). HDST

may help discriminate adrenal forms of CS from CD. If there is a suppression, an adrenal etiology would be unlikely. However, a lack of suppression does not rule out ACTH dependent CD. In a normal pregnancy, ACTH response to CRH is known to be weaker due to increased resistance in the third trimester. Ovine CRH (Food and Drug Administration-FDA- category C) should only be used in pregnancy if indicated (6, 7). In a pregnant woman with mild cushingoid features, Ragonese *et al.* (26) reported that human CRH and desmopressin stimulated ACTH tests are useful to confirm the diagnosis of CD during the first trimester and after delivery. Lindsay *et al.* (14) recommended plasma ACTH level and HDST with adrenal ultrasonography as an initial step in the differential diagnosis of pregnant patients.

MRI is contraindicated during the first trimester due to the potential teratogenicity, but it can be safely performed after the second trimester (27, 28). Moreover, lesions can be difficult to detect due to the pituitary hyperplasia in pregnancy and the low sensitivity of non-contrast MRI. However, the administration of gadolinium during pregnancy (FDA category C) has not been proven to be safe (14, 27, 29). Our patient underwent non-contrast MRI in the second trimester. An asymmetric pituitary gland with suspect lesion in the right side without discrete mass was visualised. If there is a lesion less than 6 mm on the pituitary MRI, further invasive techniques are required for diagnosis. Inferior petrosal sinus sampling using direct jugular approach is not recommended during pregnancy because of radiation exposure, increased thrombotic event incidence and limited experience (14, 30). Further evaluation was postponed until after delivery, since our patient did not have any serious complications of CD.

The most common complications of CS in pregnancy are hypertension, impaired glucose tolerance and DM as seen in our patient. In a small number of cases, pregnancy is associated with poor wound healing, opportunistic infections, osteoporosis, fracture, severe psychiatric complications, maternal cardiac failure, pre-eclampsia, pulmonary edema and death (3, 19, 31). Our patient developed none of these complications and her spontaneous pregnancy was an evidence that she did not have severe hypercortisolism. Fetal complications include early spontaneous abortions, premature labor (20 to 38 weeks of gestation), IUGR and neonatal complications such as hypocortisolemia and hypoglycemia (1, 3, 6, 13, 14, 32). Consequently, a pregnancy complicated by CS is a high-risk obstetric

condition. However, obstetric complications were not observed in our patient, which was probably because she had cyclic CD. A similar case has been previously reported (16).

These possible complications necessitate early diagnosis and appropriate treatment of CS in pregnancy. The decision for treatment depends on the severity of hypercortisolism and gestational age at time of diagnosis. Adrenalectomy is useful in adrenal CS with a live birth ratio of 87% (32). Transsphenoidal adenomectomy is also the gold standard treatment of CD in pregnancy, it is applied with success during mid-pregnancy (2, 6, 7-9, 14, 33, 34). Medical therapy is the second choice of treatment after surgery. It can be considered in case of serious hypercortisolism or persistent disease after surgery. The widely used drug for medical treatment is metyrapon and it has had no adverse effects on maternal hepatic function or fetal development. However, this drug may exacerbate hypertension and cause progression to preeclampsia, which may limit its use (14, 35). Despite known antiandrogenic effects of ketoconazole (FDA category C), it has been used successfully in some pregnancies without adverse events. It was recently reported that treatment with ketoconazole during the critical period of organogenesis did not cause congenital birth defects on the fetus of two women with CD (9, 36, 37). Moreover, cases treated with cyproheptadine, aminoglutethimide and mitotane have been reported (14, 38-40). Cyproheptadine was not found to be effective and therefore is not recommended; aminoglutethimide and mitotane are contraindicated due to fetal masculinization and teratogenicity (38-40). A patient with known CD maintained on high-dose cabergoline treatment throughout pregnancy was also reported (41).

Conservative approach can also be preferred if hypercortisolemia is not severe. Only complications of the CD, such as DM, hypertension and glucose intolerance are treated in these cases, as was the case with our patient, who only received insulin treatment for DM. Lindsay *et al.* (14) reported live birth in 59 of 74 patients who received conservative treatment. There was no statistically significant difference between the medically and conservatively treated groups. Despite high abortion and ectopic pregnancy rates, patients with mild CD are likely to have spontaneous pregnancies with favorable outcomes (2, 10, 26).

Earlier recognition and treatment certainly improves outcome. A multidisciplinary approach consisting of endocrinology, obstetrics, anesthesiology

and endocrine surgery is recommended. Due to the rarity of the pathology, guidelines for diagnosis and treatment are not available. The decision for treatment depends on the severity of hypercortisolism and gestational age at time of diagnosis. In cases where maternal and fetal complications are mild, conservative approach may be used and specific treatment can be postponed until after delivery. The mother and the fetus must be monitored closely and frequently for cardiovascular and metabolic parameters at all times.

Conflict of interest

The authors declare that they have no conflict of interest.

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