Case Report
Progestin induced secondary diabetes mellitus and adrenal insufficiency: a case report

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Abstract: We report a case of a 34-year-old woman diagnosed as atypical endometrial hyperplasia and was administered megestrol acetate (MA) 160 mg qd. One month later, she presented palpitation, sweating, tremor, head pain and body weight gain (4 kg within a month). After 3 months treatment, her symptoms above worsened and weight gain continued (22 kg within 4 month). We altered the treatment regimen to medroxyprogesterone acetate (MPA) 500 mg daily oral but symptoms gradually worsened. Laboratory studies showed cortisol (ug/dl) and adrenocorticotrophic-hormone (ACTH, pg/ml) rhythm as: 8 a.m. 2.03; 23.04; 4 p.m. 0.27; 2.72; 0 a.m. 0.19; 1.95; Extended oral glucose tolerance test (OGTT, mmol/L) as: 0 h 4.59; 0.5 h 8.86; 1 h 9.83; 2 h 11.3; 3 h 7.21; 4 h 3.95; 4.5 h 2.5. After endometrial curettage, we treated her with acarbose 50 mg tid and pioglitazone 15 mg qd, as well as MPA 500 mg qd for 3 months, the blood glucose level of the patient was under control and menstrual cycle was regular. Clinicians should be aware of the potential effects of progestin on the hypothalamic-pituitary-adrenal (HPA) axis and glucose tolerance.

Keywords: Megestrol, medroxyprogesterone, diabetes mellitus, adrenal insufficiency

Introduction
Megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are progestin which are synthetic progesterational agent. Both MA and MPA are usually used for menopausal hormone replacement, endometriosis, and as palliative treatment of endometrial cancer, breast cancer, and prostate cancer. In addition to the effects on the progesterone receptor, MA and MPA also bind the glucocorticoid receptor. Some patients receiving MA and MPA therapy have been reported to develop clinical features of glucocorticoid excess, while others have experienced the clinical syndrome of cortisol deficiency. We describe a patient who presented adrenal insufficiency and new-onset diabetes mellitus induced by MA and MPA.

Case description
In January 2014, a 34-year-old woman presented to our hospital with a 15-day history of irregular vaginal bleeding. Vaginal ultrasound revealed endometrial thickness, measuring 13.2 mm, and reflecting heterogeneity. Given hysteroscopy and diagnostic curettage, endometrial pathology indicated complex atypical hyperplasia. She was administered 160 mg/d megestrol acetate. A month later, the patient presented with palpitation, sweating, tremor, head pain, increased appetite, and body weight gain (4 kg within a month). After three months of this treatment, she underwent subsequent hysteroscopy and diagnostic curettage which indicated after progesterone treating response accompanied by complex atypical hyperplasia with small focal metaplasia. Considering results of pathology and weight gain, we altered the treatment regimen to 500 mg daily oral medroxyprogesterone acetate instead of megestrol acetate, but palpitations, sweating and other symptoms gradually worsened and new symptoms of bloating, belching after meals, and continued weight gain (22 kg within 4 month) evolved. In mid-May 2014, she com-
plained of weight gain in the endocrinological clinic. Physical examination indicated uniformity of obesity without purple stripes and altered pigmentation on the skin. Computer tomography (CT) scans of abdomen and magnetic resonance imaging (MRI) of pituitary showed normal. Laboratory studies revealed that cortisol concentrations and adrenocorticotropic hormone (ACTH) levels were suppressed (cortisol (μg/dl), ACTH (pg/ml) rhythm: 8 a.m. 2.03; 23.04; 4 p.m. 0.27; 2.72; 12 a.m. 0.19; 1.95). Extended OGTT (fingertip glucose mmol/L) was recorded as follows: 0 h 4.59; 0.5 h 8.86; 1 h 9.83; 2 h 11.3; 3 h 7.21; 4 h 3.95; 4.5 h 2.5; Urinary free cortisol level (24 h) was 235.71 μg.

Glycated hemoglobin was measured at 6.6%. Initial diagnosis was secondary diabetes and adrenal insufficiency with atypical endometrial hyperplasia.

The patient was administered acarbose 50 mg tid and pioglitazone 15 mg q.d. Upon this new treatment, her serum glucose concentration was gradually controlled; palpitations, sweating and tremor were improving. Since there was no clinical symptom of adrenal insufficiency, cortisol was not included in the treatment regimen. After the patient was discharged, she continued taking acarbose and pioglitazone, and was instructed to follow-up.

She underwent hysteroscopy and diagnostic curettage the third time in July 2014 which indicated significant stromal decidual changes and few glands. To prevent adrenal crisis, we administered 100 mg intravenous hydrocortisone during hysteroscopy and diagnostic curettage practice. The patient continued taking oral medroxyprogesterone acetate 500 mg q.d in addition to acarbose 500 mg tid and pioglitazone 15 mg q.d for three months then withdrawal. Currently, the patient has no complaints of palpitation, sweating, tremor, or other symptoms. In addition, the serum glucose is under-control and there is no evidence of abnormal vaginal bleeding.

Discussion

Progestin displayed considerable affinity towards the glucocorticoid receptor in various cells, as well as glucocorticoid-like activity both in vitro and in vivo [1-3], which can cause weight gain, high serum glucose, head pain, and other side effects. As compared to the reference compound dexamethasone (relative receptor binding affinity defined as 100%), megestrol acetate and medroxyprogesterone acetate were found to display a considerable binding affinity towards the receptor (46% and 42%, respectively). The relative binding affinity of the naturally occurring ligand, cortisol, to the receptor was clearly lower (25%) [4]. High-dose and long-term treatment with these medications can even cause Cushing syndrome and suppress cortisol concentrations which can lead to adrenal insufficiency [5, 6]. Exacerbation of preexisting or new-onset diabetes mellitus are other adverse effects related to this activity [7]. Megestrol acetate and medroxyprogesterone caused adrenal insufficiency or diabetes has previously been reported [6-9]. However, there is no report about progestin-induced both of adrenal insufficiency and diabetes in one patient when treating atypical endometrial hyperplasia. Her low concentrations of cortisol and ACTH match adrenal insufficiency diagnosis. Adrenal insufficiency usually manifested as fatigue or gait difficulties, excessive thirst, or gastrointestinal symptoms such as anorexia, abdominal pain, nausea, vomiting, diarrhea or constipation. In addition, individuals with adrenal insufficiency may suffer from hypotension and electrolyte disorders. The patient’s symptoms improved after taking hypoglycemic drugs, which indicated no clinical manifestations of adrenal insufficiency, so cortisol was not indicated for treatment. The suppression of the pituitary-adrenal-axis appears to be asymptomatic in this patients, because these symptoms could be justified by the ability of MA and MPA to act as a glucocorticoid agonist and to replace the endogenous activity under basal conditions. These adverse reactions of our patient occurred after progestin application, and coincided with known adverse reactions of progestin. The disease itself can’t explain these symptoms. We believe that our patient developed iatrogenic diabetes mellitus and adrenal insufficiency secondary to the administration of MA and MPA. For patients with atypical hyperplasia, high-dose progestosterone one treatment (at least 6 months) is suggested, so close monitoring of adverse reactions of progestin is crucial. We would also like to emphasize that since these progestins can cause adrenal suppression, it is important to withdraw therapy gradually in order to allow the hypothalamic pituitary adrenal axis to recover.
And it seems prudent to consider providing exogenous glucocorticoid therapy to patients receiving MA and MPA during times of significant stress such as severe infection.

In conclusion, we report a case of MA and MPA caused secondary diabetes mellitus and adrenal insufficiency. Deep understanding of progestin may improve assessment and management of patients, particularly in those receiving high-dose, long-term treatment. Clinicians should be aware of the potential effects of MA and MPA on the hypothalamic-pituitary-adrenal (HPA) axis and glucose tolerance.

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