

## Brief Report

## LEUPROLIDE ACETATE THERAPY IN LUTEINIZING HORMONE-DEPENDENT CUSHING'S SYNDROME

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**C**ORTICOTROPIN-INDEPENDENT Cushing's syndrome is usually caused by cortisol-secreting adrenal adenomas, carcinomas, or (rarely) bilateral adrenal hyperplasia. In some patients with this syndrome, the excess secretion of cortisol is caused by abnormal adrenal expression and function of receptors for various hormones, including gastric inhibitory polypeptide,<sup>1-6</sup> vasopressin,<sup>7-9</sup>  $\beta$ -adrenergic agonists,<sup>10</sup> and interleukin-1.<sup>11</sup> These findings suggest that diverse other hormone receptors could be implicated in other patients.<sup>12</sup>

We describe a woman with bilateral adrenal hyperplasia and corticotropin-independent Cushing's syndrome that was clinically manifested transiently during her pregnancies and became constant only after menopause. The patient's cortisol secretion was stimulated by luteinizing hormone and chorionic gonadotropin and by drugs that activate serotonin 5-hydroxytryptamine (HT<sub>4</sub>) receptors. Long-term suppression of luteinizing hormone secretion by the administration of leuprolide acetate every four weeks led to complete reversal of Cushing's syndrome in the patient.

## CASE REPORT

A 63-year-old woman presented with a 12-month history of hypertension, numbness and proximal-muscle weakness of the lower extremities, hot flashes, and a decrease in concentration and memory. Her usual weight was 45 to 50 kg until menopause at 52 years of age; it then increased progressively to 73 kg. She had gained between 18 and 22 kg during each of four full-term pregnancies, at which time she had a cushingoid distribution of fat but no hypertension, purple skin striae, or hirsutism; all her children were normal. Post partum, her weight had rapidly returned to base line, and she had anorexia, nausea, and fatigue, all of which subsided within two to three months. She had undergone hysterectomy and bilateral oophorectomy at 61 years of age because of uterine prolapse. There was no family history of adrenal disease. Her height was 1.59 m, her blood pressure was 198/102 mm Hg,

and her heart rate was 80 beats per minute. The patient had central obesity, mild facial plethora and hirsutism, supraclavicular fat pads, proximal muscle weakness, and decreased vibratory sensation in the lower legs, but no abdominal striae. She was taking an angiotensin-converting-enzyme inhibitor, a thiazide diuretic, and estrogen-replacement therapy; these medications were discontinued three days before the studies described below.

The initial evaluation, which took place in March and April 1997, revealed a urinary cortisol excretion of 279  $\mu$ g per day (770 nmol per day; normal, 20 to 90  $\mu$ g per day [55 to 248 nmol per day]). The patient's morning plasma corticotropin concentration was less than 5 pg per milliliter (1 pmol per liter; normal, 9 to 52 pg per milliliter [2 to 11 pmol per liter]). Her plasma cortisol concentration was 28.4  $\mu$ g per deciliter (784 nmol per liter) at 8 a.m. and 18.4  $\mu$ g per deciliter (508 nmol per liter) at 8 p.m.; it was 24.7  $\mu$ g per deciliter (681 nmol per liter) in the morning after the oral administration of 1 mg of dexamethasone at midnight and was not suppressed by 4 mg of dexamethasone administered intravenously. Plasma aldosterone and renin values obtained with the patient supine and upright were normal. An abdominal computed tomographic scan revealed bilateral macronodular adrenal hyperplasia, with nodules measuring up to 4 by 3.5 cm on the right and 2.5 by 4 cm on the left.

## METHODS

## Clinical Studies

The protocol used to detect the presence of abnormal adrenal hormone receptors in patients with adrenal Cushing's syndrome has been described previously.<sup>13</sup> We measured plasma corticotropin, cortisol, and other steroids in the 63-year-old patient after she had fasted overnight and at 30-to-60-minute intervals for up to 3 hours after we performed various tests and administered several hormones and drugs (Table 1). For comparison, two control women, both 33 years old and taking oral contraceptives, were given intravenous injections of 300 U of recombinant human luteinizing hormone (LHadi, Serono Canada, Oakville, Ont.), to determine the effects of a short-term, rapid increase in plasma luteinizing hormone concentrations on plasma cortisol concentrations.

Our studies were approved by the institutional ethics committee, and written informed consent was obtained from all subjects.

## Assays

We measured plasma cortisol and estradiol by immunofluorometric assay (Immuno I System, Bayer, Tarrytown, N.Y.), renin by immunoradiometric assay, corticotropin by Allegro immunoradiometric assay (Nichols Diagnostics, San Juan Capistrano, Calif.), and aldosterone, free testosterone, and dehydroepiandrosterone sulfate by radioimmunoassay.

## RESULTS

There were no significant increases in the patient's plasma cortisol concentrations while she was upright, after ingestion of a mixed meal (a standard mixture of proteins, fats, and carbohydrates), or after administration of thyrotropin-releasing hormone, glucagon, arginine vasopressin, or insulin (Table 1). Plasma cortisol concentrations increased to 2.1 times base line within 90 minutes after intravenous injection of gonadotropin-releasing hormone, whereas the plasma luteinizing hormone concentration increased from 26 to 116 U per liter and the plasma follicle-stimulating hormone concentration increased from 52 to 80 U per liter. In addition, the administration of cisapride and metoclopramide, which are serotonin 5-HT<sub>4</sub> receptor agonists, resulted in plasma cortisol

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**TABLE 1.** IN VIVO MODULATION OF CORTISOL SECRETION IN A PATIENT WITH CUSHING'S SYNDROME AND CORTICOTROPIN-INDEPENDENT MACRONODULAR ADRENAL HYPERPLASIA.\*

TEST	PLASMA CORTISOL AT BASE LINE	PEAK PLASMA CORTISOL	PEAK VALUE AS A PERCENTAGE OF BASE-LINE VALUE
	μg/dl		
Upright posture	23.3	24.8	106
Mixed meal	24.5	23.3	95
Cosyntropin, 250 μg IV	15.3	138.7	907
GnRH, 100 μg IV	18.0	38.6	214
TRH, 200 μg IV	29.1	18.0	62
Glucagon, 1 mg IV	19.8	16.1	81
Arginine vasopressin, 10 U IM	19.3	17.5	91
Insulin, 0.25 U/kg of body weight IV	30.6	23.5	77
Cisapride, 10 mg orally	15.9	76.0	478
Metoclopramide, 10 mg orally	22.2	57.1	257
Chorionic gonadotropin, 10,000 U IM	25.2	49.6	197
FSH, 300 U IM	30.1	29.6	98
Dexamethasone, 4 mg IV	25.4	22.4	88

\*To convert plasma cortisol values to nanomoles per liter, multiply by 27.59. IV denotes intravenously, GnRH gonadotropin-releasing hormone, TRH thyrotropin-releasing hormone, IM intramuscularly, and FSH follicle-stimulating hormone.

concentrations that were 4.8 and 2.6 times the base-line value, respectively, at 120 minutes. Plasma corticotropin concentrations remained undetectable during all these tests, and exogenous cosyntropin increased the plasma cortisol concentration (Table 1). Daily urinary cortisol excretion increased substantially after the administration of cosyntropin, cisapride, metoclopramide, and chorionic gonadotropin (Fig. 1).

To determine whether the increase in cortisol production resulting from the administration of gonadotropin-releasing hormone was mediated by the stimulation of endogenous luteinizing hormone or follicle-stimulating hormone or directly by gonadotropin-releasing hormone, plasma cortisol was measured after the intramuscular administration of chorionic gonadotropin (A.P.L., Wyeth-Ayerst, Montreal) and also after the intramuscular administration of follicle-stimulating hormone (Fertinorm HP, Serono Canada). The patient's plasma cortisol concentration almost doubled within four hours after the administration of chorionic gonadotropin, whereas follicle-stimulating hormone had no significant effect (Table 1). These tests were conducted in June.

After the intramuscular administration of 3.75 mg of leuprolide acetate (Lupron Depot, Tap Pharmaceuticals, North Chicago, Ill.) on July 1, the plasma luteinizing hormone concentration increased from 25 to 95 U per liter, the plasma follicle-stimulating hor-

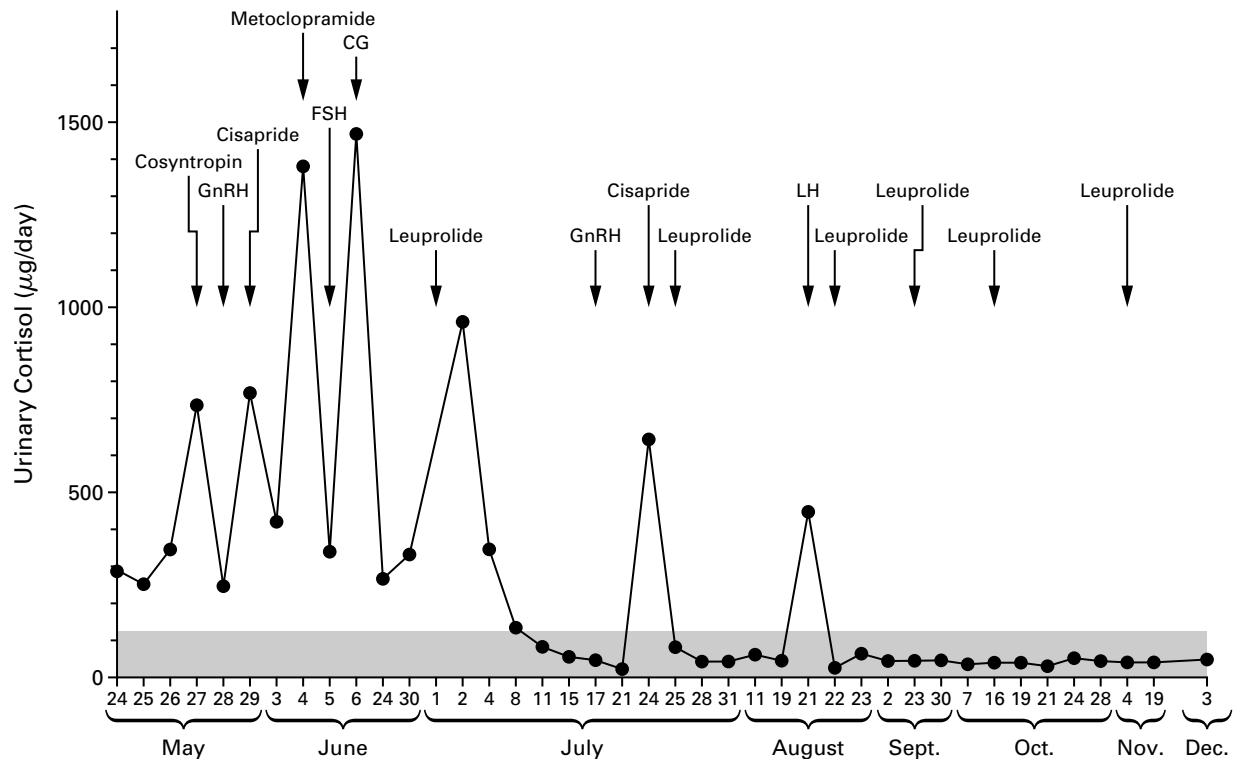
mone concentration increased from 49 to 81 U per liter, and the plasma cortisol concentration increased from 17.4 to 34.0 μg per deciliter (479 to 939 nmol per liter) in six hours, whereas plasma corticotropin remained undetectable. Urinary cortisol excretion increased during the first day after the administration of leuprolide acetate and then gradually declined to normal within one week (Fig. 1). At that time, the morning plasma cortisol concentration was 6.3 μg per deciliter (173 nmol per liter); there were no increases in plasma cortisol, urinary cortisol excretion, plasma luteinizing hormone, or plasma follicle-stimulating hormone after the intravenous administration of gonadotropin-releasing hormone (Fig. 1). However, cisapride was still able to increase plasma cortisol concentrations and urinary cortisol excretion (Fig. 1).

Subsequently, the patient was given 3.75 mg of leuprolide acetate every four weeks. These injections were not followed by increases in plasma or urinary cortisol values because there was no increase in plasma luteinizing hormone concentrations (Fig. 1). In August, eight weeks after we initiated therapy with leuprolide acetate, the intravenous administration of recombinant human luteinizing hormone resulted in an increase in the plasma cortisol concentration to six times base line (Fig. 2) and an increase in urinary cortisol excretion (Fig. 1).

With respect to other adrenal steroids, plasma aldosterone concentrations increased in response to cisapride and cosyntropin but not in response to luteinizing hormone. Plasma free testosterone concentrations increased in response to all three substances, whereas serum dehydroepiandrosterone sulfate concentrations increased slightly in response to cisapride and cosyntropin. Plasma estradiol concentrations increased only in response to luteinizing hormone.

The administration of luteinizing hormone to the two normal women in whom the secretion of endogenous luteinizing hormone had been suppressed resulted in delayed increases in plasma cortisol concentrations to 38 percent and 90 percent above the base-line value at 240 to 300 minutes. These increases were accompanied by parallel increases in plasma corticotropin concentrations (data not shown). The suppression of endogenous corticotropin by pretreatment with dexamethasone in one of these women prevented the delayed increase in plasma cortisol after intravenous injection of luteinizing hormone (Fig. 2).

Long-term treatment of the patient with Cushing's syndrome with 3.75 mg of leuprolide acetate given intramuscularly every 4 weeks kept urinary cortisol excretion within the normal range (32 to 62 μg [89 to 172 nmol] per day) for the next 24 months. Within six months after therapy was initiated, the patient had normal morning and evening plasma cortisol concentrations and a normal response to insulin-induced hypoglycemia. Her weight decreased to 68 kg in six months, and her blood pressure became normal with-



**Figure 1.** Urinary Cortisol Excretion in a Patient with Cushing's Syndrome and Bilateral Macronodular Adrenal Hyperplasia during Initial Studies and Treatment.

The arrows indicate the days on which specific tests were performed. See Table 1 for doses of hormones and drugs and routes of administration. GnRH denotes gonadotropin-releasing hormone, FSH follicle-stimulating hormone, CG chorionic gonadotropin, and LH luteinizing hormone. Normal urinary cortisol values (18 to 120  $\mu\text{g}$  per day) are indicated by the stippled area. To convert values for urinary cortisol to nanomoles per day, multiply by 2.759.

out antihypertensive-drug therapy. Estrogen-replacement therapy was reinitiated. The size of the adrenal glands remained unchanged on abdominal computed tomography performed 12 and 24 months after the initiation of leuprolide acetate therapy. The oral administration of 10 mg of cisapride 24 months after the initiation of leuprolide acetate therapy still resulted in an increase in the plasma cortisol concentration from 11.6 to 67.4  $\mu\text{g}$  per deciliter (321 to 1860 nmol per liter).

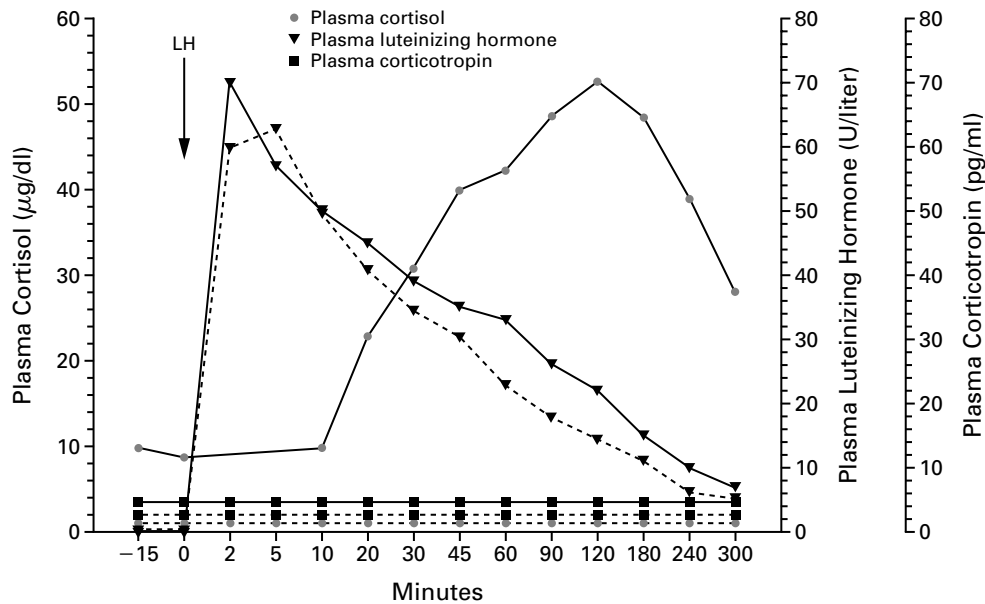
## DISCUSSION

The patient's Cushing's syndrome resulted from corticotropin-independent bilateral macronodular hyperplasia, and cortisol production was stimulated in vivo by gonadotropin-releasing hormone, luteinizing hormone, chorionic gonadotropin, cisapride, and metoclopramide. The stimulation of cortisol production by chorionic gonadotropin and luteinizing hormone but not by follicle-stimulating hormone suggests that a functional receptor for adrenocortical luteinizing hormone and chorionic gonadotropin was coupled to steroidogenesis; the lack of stimulation by gonadotropin-releasing hormone when luteinizing

hormone secretion was suppressed by the administration of leuprolide acetate rules out the presence of an adrenal gonadotropin-releasing hormone receptor.

The luteinizing hormone and chorionic gonadotropin receptor activates adenylyl cyclase and phospholipase C to stimulate gonadal steroidogenesis.<sup>14,15</sup> The receptor is expressed mainly in gonadal tissues but also in other tissues, including the uterus, fallopian tubes, placenta, brain, hypothalamus, and prostate.<sup>16</sup> This receptor has also been identified in the zona reticularis of the human adrenal cortex,<sup>17</sup> and chorionic gonadotropin stimulates the secretion of dehydroepiandrosterone sulfate in human fetal adrenal cells.<sup>18</sup> The aberrant expression of luteinizing hormone and chorionic gonadotropin receptor was detected previously in in vitro studies of adenomas that secreted cortisol<sup>19</sup> or androgen<sup>20</sup> and in a carcinoma that secreted androgen and estrogen<sup>21</sup>; chorionic gonadotropin or gonadotropin-releasing hormone stimulated androgen production in vivo in adrenal tumors.<sup>20-24</sup>

Serotonin is produced by intraadrenal mast cells in humans and can regulate glucocorticoid production through a paracrine mechanism<sup>25,26</sup>; these effects are mediated by the 5-HT<sub>4</sub>-receptor subtype, which is ex-



**Figure 2.** Plasma Cortisol, Luteinizing Hormone, and Corticotropin Concentrations after the Intravenous Administration of 300 U of Recombinant Human Luteinizing Hormone (LH; Arrow) in the Patient with Cushing's Syndrome and Corticotropin-Independent Bilateral Macronodular Adrenal Hyperplasia (Solid Lines) and a Control Woman (Dashed Lines). In the patient with Cushing's syndrome and bilateral macronodular adrenal hyperplasia, the test was performed after endogenous luteinizing hormone secretion had been suppressed by the administration of leuprolide acetate. In the control woman, endogenous luteinizing hormone secretion was suppressed by an oral contraceptive, and corticotropin was suppressed by dexamethasone. To convert values for plasma cortisol to nanomoles per liter, multiply by 27.59; to convert values for plasma corticotropin to picomoles per liter, multiply by 0.22.

pressed mainly in cells from the adrenal zona glomerulosa but also in cells from the zona fasciculata.<sup>25,26</sup> 5-HT<sub>4</sub>-receptor agonists are potent stimulators of aldosterone secretion in humans; they are weak stimulators of cortisol secretion in vitro but do not stimulate cortisol secretion in normal subjects.<sup>26</sup> The stimulation of plasma cortisol in our patient after the administration of cisapride and metoclopramide was proportional to the respective affinity of the drugs for the 5-HT<sub>4</sub> receptor<sup>25</sup>; no such response to cisapride was found in 6 patients with bilateral adrenal hyperplasia, 10 with unilateral adenoma, and 1 with carcinoma and corticotropin-independent Cushing's syndrome.<sup>27</sup>

The bilateral nature of the adrenal hyperplasia in our patient suggests that abnormal tissue-specific expression of the luteinizing hormone and chorionic gonadotropin receptor and the 5-HT<sub>4</sub> receptor occurred during embryogenesis, but the syndrome became clinically evident only after sustained increases in endogenous secretion of the two gonadotropins either during the pregnancies or after menopause. Transient corticotropin-independent Cushing's syndrome during pregnancy with resolution after delivery has been described previously in women with adrenal adenomas<sup>28</sup> and women with mild bilateral adrenal hyperplasia<sup>29,30</sup>; in one case, the administration of cho-

ronic gonadotropin increased urinary 17-hydroxycorticosteroid excretion.<sup>31</sup>

The identification of ectopic adrenal receptors could eventually lead to diverse drug treatments as alternatives to adrenalectomy for patients with adrenal Cushing's syndrome.<sup>2,10</sup> In the present case, the suppression of endogenous luteinizing hormone secretion by leuprolide acetate controlled hypercortisolism and made bilateral adrenalectomy unnecessary. A gonadotropin-releasing hormone analogue has proved effective in a patient with a testosterone-secreting ovarian tumor.<sup>32</sup> Despite complete suppression of endogenous luteinizing hormone secretion, cortisol insufficiency did not develop in our patient. Perhaps basal cortisol production was maintained by stimulation of the abnormal 5-HT<sub>4</sub> receptor by serotonin; this hypothesis could not be proved, however, because of the lack of availability of specific antagonists. The absence of regression of bilateral adrenal hyperplasia despite long-term suppression of luteinizing hormone secretion may indicate that the hyperplasia is maintained by abnormal function of the 5-HT<sub>4</sub> receptor or that the aberrant receptors regulate steroidogenesis but not cell proliferation.

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