

The Effect of Long Acting Glucocorticoids on Menstrual Abnormalities in Patients with Virilizing Congenital Adrenal Hyperplasia*

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ABSTRACT. Amenorrhea or oligomenorrhea occurs in more than 25% of young women with virilizing congenital adrenal hyperplasia due to 21-hydroxylase deficiency who are treated with conventional glucocorticoid therapy. In four such patients, we studied the variation in plasma concentration of ACTH, 17-hydroxyprogesterone (17-OHP), estradiol (E₂), estrone, testosterone (T), dehydroepiandrosterone and its sulfate, androstenedione, and progesterone before and at frequent intervals after the administration of the patients' usual dose of oral glucocorticoids. We found that plasma ACTH, 17-OHP, and T were usually increased above the normal range early in the morning before the first daily dose of medication; plasma dehydroepiandrosterone and its sulfate were decreased below the normal range for the patient's pubertal stage; and androstenedione, estrone, and E₂ were within the normal range. Two of the four patients had low basal plasma LH and

impaired LH response to LRF. Administration of a long acting glucocorticoid (dexamethasone) to three patients, and methylprednisolone to one, resulted in continuous suppression of T into the normal range in all patients, in spite of continued abnormally increased concentration of ACTH and 17-OHP in two patients. In three patients, E₂ concentrations were increased when a long acting glucocorticoid was given. In all four patients, menses began or became more regular during treatment with the long acting glucocorticoid. We conclude that a long acting glucocorticoid is useful in the management of menstrual abnormalities in adolescent patients with congenital adrenal hyperplasia who have attained their adult height, and that monitoring the concentration of serum T in them is a valuable but not infallible procedure for assessing the effectiveness of therapy. (*J Clin Endocrinol Metab* 47: 1208, 1978)

IN ORDER to achieve normal growth and development in patients with virilizing congenital adrenal hyperplasia (CAH), optimal management balances adequate adrenal suppression with glucocorticoids against the undesirable effects of excess glucocorticoid therapy. Despite early diagnosis and institutions of treatment, some patients with CAH fail to achieve either an adult height which is compatible with their genetic potential or normal menses. Of the adolescent female patients being treated for virilizing CAH in our clinic, 25% had not had the onset of menses by 17 yr (1), similar to the findings of Jones and Verkauf (2) and Klingensmith *et al.* (3)

In an attempt to elucidate the factors which

may contribute to delayed menarche and menstrual irregularity in this condition, we have studied the pattern of circulating steroids, ACTH, and gonadotropins in four patients. The results suggest that even in patients without signs of progressive virilization, an increased concentration of plasma testosterone in the early morning or in multiple daytime specimens may be associated with an abnormal menstrual history. Treatment with a more potent, long acting glucocorticoid has resulted in more continuous suppression of plasma testosterone, associated with initiation or restoration of cyclic menses in four patients.

Patients and Methods

The four patients selected for this study had CAH due to 21-hydroxylase deficiency with salt loss. Three patients (patients 1, 3, and 4; Table 1) were pubertal but had not had menses; one (patient 2) had menarche at 13 yr but had oligomenorrhea after the age of 15. The diagnosis of 21-hydroxylase deficiency was made in early infancy in all patients, although patient 3 was treated intermittently until

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2 3/12 yr. Clinical details are provided in Table 1. Before testing, all patients were on a dose of glucocorticoid which had not been changed in several years (Table 1). Growth rate had been normal, and symptoms of virilization were consistently suppressed. Urinary ketosteroids had been stable and, with occasional exceptions, had been under 15 mg/day (the upper limit of normal in our laboratory for postpubertal females).

Plasma ACTH, testosterone, 17-hydroxyprogesterone (17-OHP), estrone (E_1), and estradiol (E_2) were measured at frequent intervals after the first morning dose of glucocorticoid. Plasma concentrations of dehydroepiandrosterone (DHEAS) and its sulfate (DHEA), androstenedione, and progesterone were also measured in selected samples. The response of pituitary gonadotropes to synthetic LRF was used to assess the hypothalamic-pituitary-ovarian axis. All determinations were made by RIA by previously described methods (4–10).

Study 1 was performed while the patients were taking their usual dose of glucocorticoid and was the subject of a previous report (1). All patients had a normal gynecological examination with no evidence of enlarged ovaries or an adnexal mass. Immediately after study 1, the medication of each patient was changed to a longer acting glucocorticoid (Table 1). The minimum initial dose of dexamethasone was 0.25 mg twice daily, which was

increased sequentially (0.5 and 0.75 mg twice daily) if menses did not occur after 4-month intervals. During the ensuing 6 months, a regular menstrual pattern was established in patients 1–3 and after 1 yr in patient 4. Seven to 15 months after study 1, a second study compared the effect of longer acting glucocorticoid preparations on the same plasma hormone concentrations measured during study 1. Again, frequent blood samples were taken before and after the first morning dose of glucocorticoid to measure ACTH, testosterone, E_1 , E_2 , and 17-OHP, with determinations of DHEAS, DHEA, androstenedione, and progesterone in selected samples.

Results

ACTH

Plasma ACTH was increased, with a range of 201–645 pg/ml before the morning administration of glucocorticoid during study 1 (Fig. 1; normal, <100 pg/ml). In all patients, ACTH decreased to the normal range within 2–3 h after glucocorticoid administration. During study 2, patients 2 and 3 had plasma ACTH concentrations >200 pg/ml before the morning dose of glucocorticoid. Patient 1, treated with dexamethasone, had suppression of

TABLE 1. Clinical data on four patients in study

	Patient no.			
	1 (8 months) ^a	2 (2 weeks)	3 (2 3/12 yr)	4 (2 weeks)
Study 1				
Age (yr)	13 7/12	16 11/12	13 3/12	19 3/12
Ht	149.4 ^b	166.3 ^c	145.8 ^d	166.3 ^e
Wt	42.4 ^f	55.3 ^c	54.3 ^c	58.8 ^g
Bone age (yr)	15	Fused	13 9/12	Fused
17-Ketosteroids (mg/day)	7.8	10.9	7.3	10.3
Medication	MP (1 mg twice daily)	HC (30-20-30 mg)	CA (15 mg twice daily)	CA (25 mg twice daily)
Study 2				
Age (yr)	14 7/12	18	14 2/12	19 10/12
Onset breast development (yr)	10	8	10	10
Menarche (yr)	14 1/12	13	13 6/12	21 6/12
17-Ketosteroids (mg/day)	4.5		2.8	5.7
Medication	Dex (0.5 mg twice daily)	Dex (0.75 mg twice daily)	MP (1 mg twice daily)	Dex (0.25 mg twice daily)

MP, methylprednisolone; HC, hydrocortisone; CA, cortisone acetate; Dex, dexamethasone.

^a Age at diagnosis is in parentheses.

^b –2 SD.

^c Mean for age.

^d –2.5 SD.

^e –0.7 SD.

^f –1.3 SD.

^g –1.4 SD.

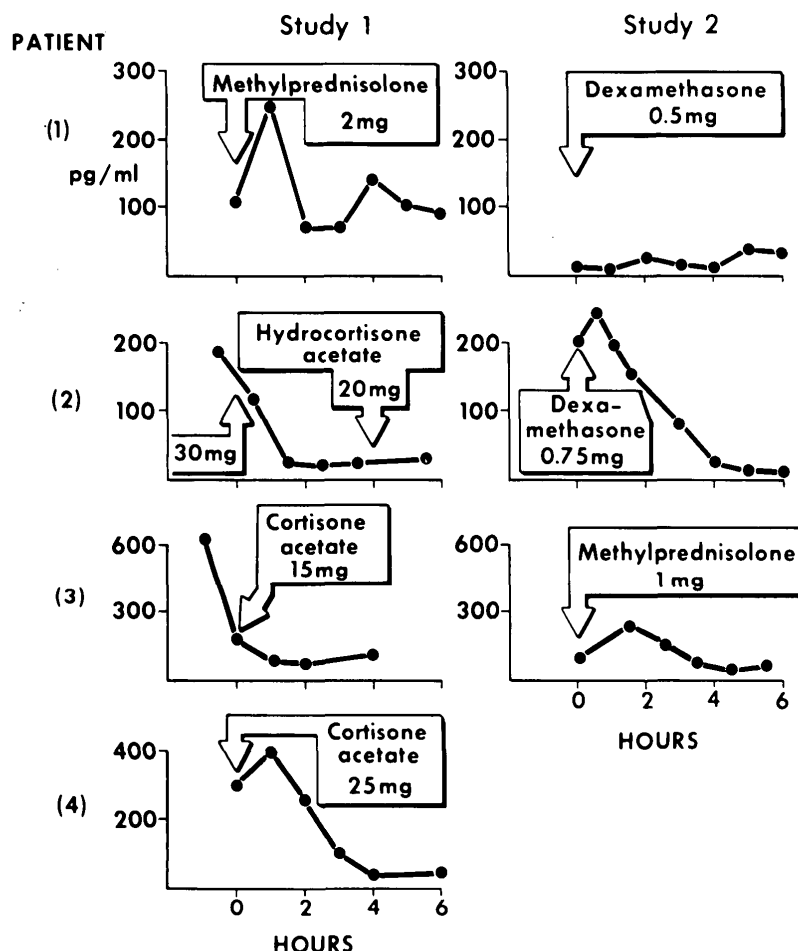


FIG. 1. Concentration of plasma ACTH in four patients with CAH after a shorter acting (left panel) and longer acting (right panel) glucocorticoid. Medication was given at time 0 between 0800–0900 h.

ACTH concentrations to <100 pg/ml before the morning dose of glucocorticoid. Again, in study 2, the increased ACTH concentrations returned to the normal range within 2–3 h (Fig. 1). Thus, longer acting glucocorticoid preparations may not suppress plasma ACTH to normal throughout a 24-h period in all patients even when given in doses that markedly suppress urinary 17-ketosteroids.

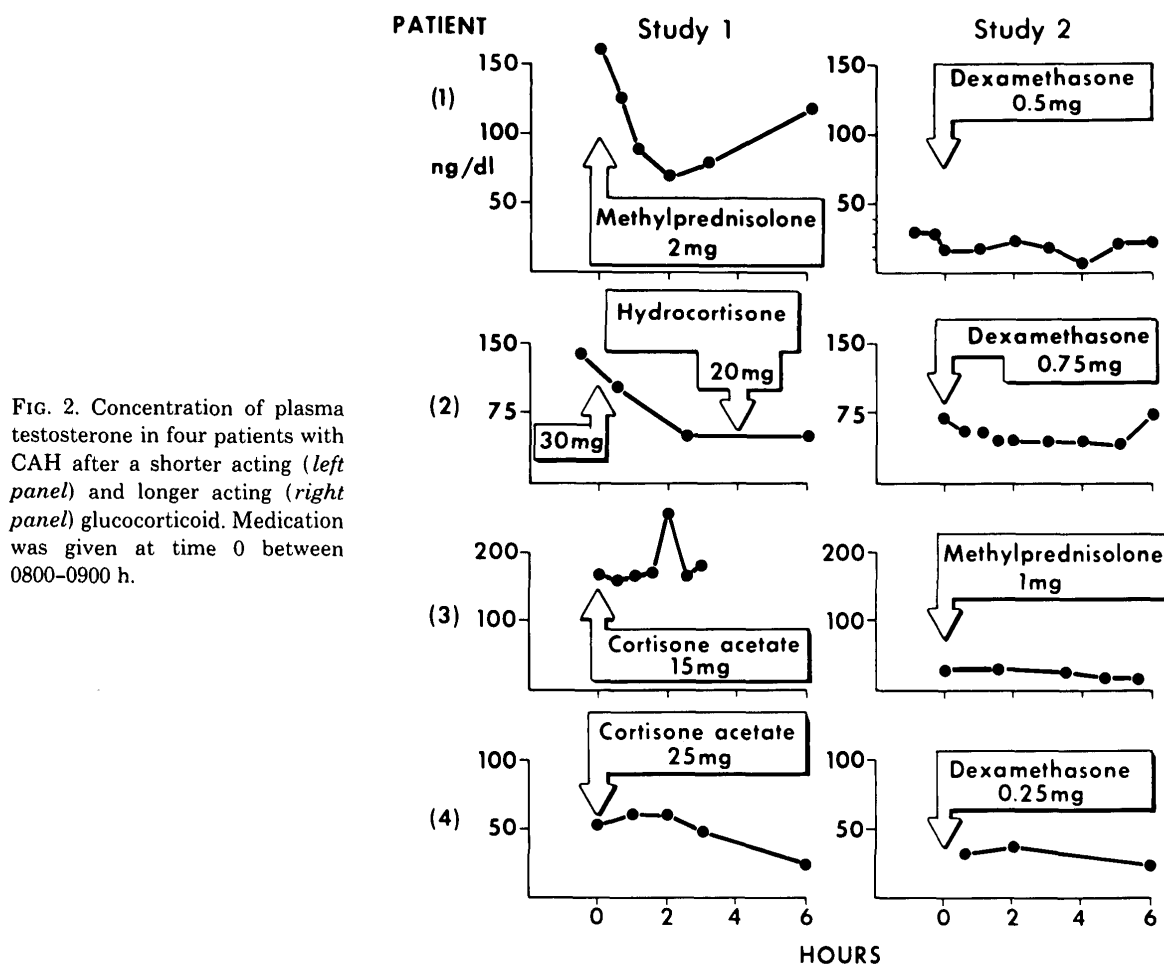
Testosterone

When treated with shorter acting glucocorticoids in study 1, concentrations of plasma testosterone were abnormally increased in three of four patients (Fig. 2), 165, 134, and 170 ng/dl in patients 1, 2, and 3, respectively, before the first morning dose of glucocorticoid. (In our laboratory, normal plasma testosterone for adult women is 30–70 ng/dl.) These levels decreased to the normal range in patients 1 and 2 within 2 h after administration

of glucocorticoid. Patient 3 had no decrease in the concentration of testosterone in study 1 but had an increase to 269 ng/dl without apparent cause. The concentration of plasma testosterone in patient 4 was not increased during study 1 but decreased after glucocorticoid administration. During study 2, all patients had normal concentrations of plasma testosterone at all times (Fig. 2), both before administration of glucocorticoid in the morning and throughout the 6 h of the study.

17-OHP

At the time of study 1, all patients had increased concentrations of plasma 17-OHP (5,000–17,000 ng/dl; Fig. 3). (The upper limit of normal in our laboratory is 150 ng/dl.) However, 2–3 h after glucocorticoid administration, levels decreased to 367–5400 ng/dl, but never reached the normal range during the testing period. 17-OHP was lower in pa-



tients 1 and 3 at the beginning of study 2 than at the beginning of study 1 (229 and 867 ng/dl, respectively), but was still above the normal range (Fig. 3). At the beginning of study 2, patients 2 and 4 had approximately the same levels as at the beginning of study 1 (15,948 and 14,050 ng/dl, respectively). Two hours after glucocorticoid administration, patients 1 and 3 had little further change in 17-OHP, but patients 2 and 4 had concentrations of 810 and 3080 ng/dl, respectively.

We conclude that long acting glucocorticoid does not reliably suppress 17-OHP to normal throughout a 24-h period. Patients who are adequately treated by other criteria may have persistence of increased 17-OHP, especially in the early morning.

E_1 and E_2

At the beginning of study 1, plasma E_2 was

in the normal range for the follicular phase of the menstrual cycle in all patients (Fig. 4). Three of four had no remarkable change in E_2 after administration of shorter acting glucocorticoid. Patient 1 had a transient unexplained increase of E_2 to 138 pg/ml after methylprednisolone during study 1.

Three patients (patients 1, 3, 4) had higher E_2 values at the beginning of study 2 than at the beginning of study 1; in addition, concentrations of E_2 increased after glucocorticoid administration in all three. During study 2, plasma E_2 levels varied from 214–329 pg/ml in patient 1, and increased from 110 to 204 pg/ml in patient 3, and from 138 to 218 pg/ml in patient 4, the explanation for which is unclear. Patient 4 was amenorrheic; hence, the high E_2 concentrations cannot be attributed to mid cycle samples. Patients 1 and 2 were having menses at approximately monthly intervals, but measurements of progesterone do not con-

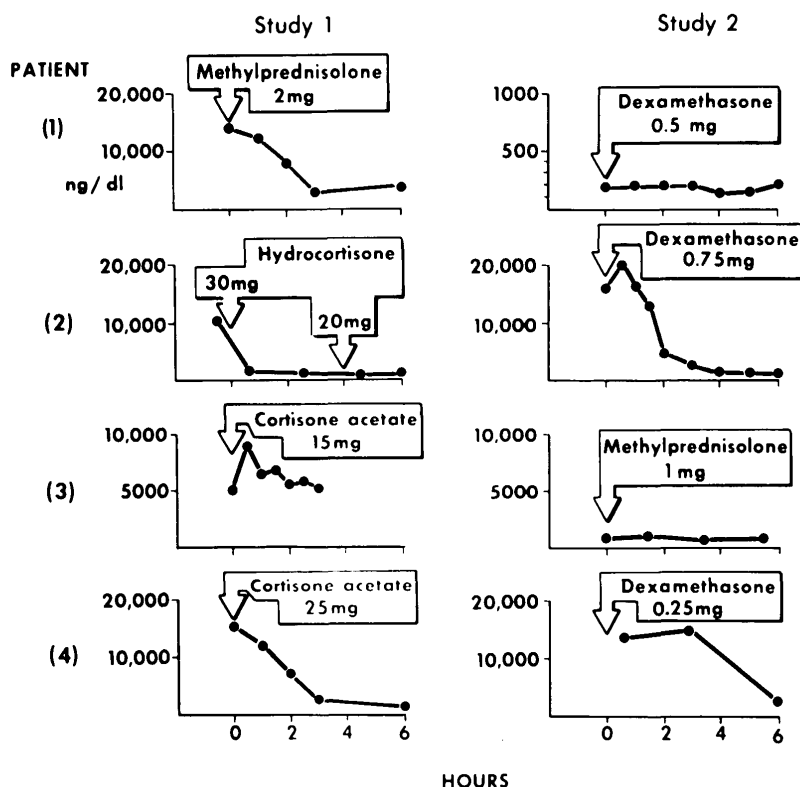


FIG. 3. Concentration of plasma 17-OHP in four patients with CAH after a shorter acting (left panel) and longer acting (right panel) glucocorticoid. Medication was given at time 0 between 0800–0900 h.

clusively define the phase of the menstrual cycle for such patients (see below).

Plasma E_1 was within the normal range of 30–160 pg/ml, except for single samples for patient 2 during study 1 (191 pg/ml) and patient 4 during study 2 (312 pg/ml). In general, levels of plasma E_2 were increased and E_1 was unaffected by a change from the short acting to a long acting glucocorticoid (Fig. 4). The increase in E_2 does not always correlate with improved menstrual history, as demonstrated by patient 4 who, at the time of study 2, remained amenorrheic in spite of increased concentrations of plasma E_2 .

LRF tests

During study 1 in patients 1 and 3, the results of the LRF test were comparable to those in female pubertal controls (Table 2). Patients 2 and 4 had low baseline LH, and the LH response to LRF was comparable to pubertal control subjects, but may be blunted when compared with menstruating adult women in the follicular phase of the cycle (11).

DHEAS, DHEA, androstenedione, and progesterone

DHEAS, DHEA, androstenedione, and progesterone were also measured in a few samples during both studies 1 and 2 (Table 3). Levels of DHEA and DHEAS were remarkably decreased compared with normal adult women (12, 13) and were generally lower during study 2 than study 1. Concentrations of these steroids in plasma fluctuated and showed neither an increasing nor decreasing trend after glucocorticoid administration. Concentration of plasma androstenedione was normal to slightly increased in the few samples in which it was measured. Again, the concentrations fluctuated and did not seem to be augmented or suppressed by glucocorticoids. Thus, DHEA, DHEAS, and androstenedione may be normal or decreased at the same time that testosterone is abnormally increased. This finding makes it unlikely that adrenal androgens other than testosterone are responsible for menstrual abnormalities in the patients in this study.

FIG. 4. Concentration of plasma E_1 and E_2 in four patients with CAH after a shorter acting (*left panel*) and longer acting (*right panel*) glucocorticoid. Medication was given at time 0 between 0800–0900 h. Note the difference in scale for studies 1 and 2 in patient 4.

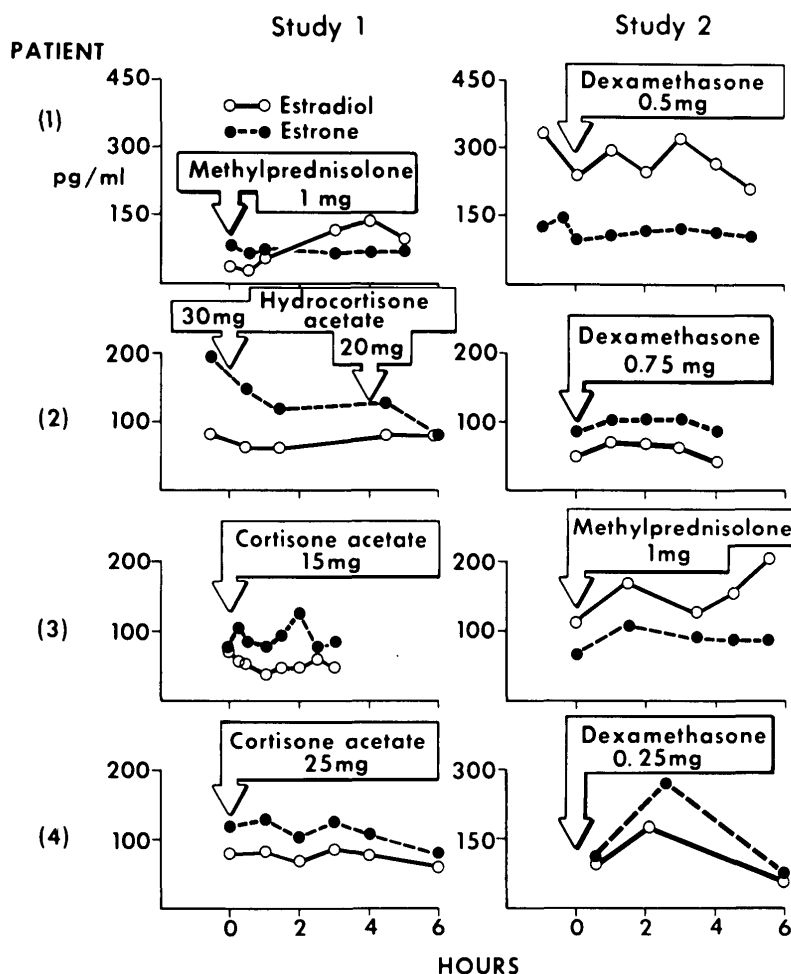


TABLE 2. Changes in plasma concentration of LH and FSH after 100 μ g iv LRF in four patients with CAH at the time of study 1

	Patient no.				Normal pu- bertal girls
	1	2	3	4	
LH					
Basal	2.4	0.8	3.8	0.5	2.15 ± 0.46
Peak	16.5	5.3	7.8	3.5	6.48 ± 0.94
Increment	14.1	4.5	4.0	3.0	4.33 ± 1.12
FSH					
Basal	2.7	2.7	4.1	2.7	2.01 ± 0.65
Peak	3.7	3.0	5.7	3.3	4.43 ± 1.24
Increment	1.0	0.3	1.6	0.6	2.42 ± 1.37

Values given are means $\pm$ SEM.

Plasma progesterone was in the normal range for the luteal phase of the menstrual cycle at some time in each patient. Since at least part of this progesterone may be of adrenal origin (14), it is difficult to determine whether ovulation had occurred by sampling

on a single day. Thus, the results of these two studies indicate that glucocorticoids with a longer duration of action than cortisone acetate are highly effective in decreasing plasma testosterone concentration to the normal range throughout a 24-h period and in increasing concentrations of plasma E_2 in patients with CAH. The decrease in concentration of testosterone in plasma occurred despite incomplete suppression of ACTH or 17-OHP. In all four young women with CAH and oligomenorrhea or amenorrhea, this decrease was associated with menarche or more regular menses.

Discussion

Delayed menarche and abnormal menstrual patterns in patients with virilizing CAH due to 21-hydroxylase deficiency could be due to

TABLE 3. Plasma concentrations of circulating DHEAS, DHEA, androstenedione, and progesterone in four study patients

	Patient no.			
	1	2	3	4
DHEAS ($\mu\text{g/dl}$)				
Study 1	21–24 (9)	25–34 (5)	20–23 (4)	24–29 (8)
Study 2	9–10 (6)	27–32 (9)	2–4 (4)	12 (1)
DHEA (ng/dl)				
Study 1		35–67 (7)		34–121 (8)
Androstenedione (ng/dl)				
Study 1	153–1170 (9)	153–352 (5)		90–183 (4)
Study 2	98–202 (9)	207–383 (9)		134–198 (7)
Progesterone (ng/ml)				
Study 1	7.3–11.5 (7)	0.2–2.3 (7)		1.5–8.6 (8)
Study 2		2.7–18.7 (9)		

The values listed represent the range of measurements at the time of studies 1 and 2, as defined in the text. The numbers in parentheses are the number of determinations.

abnormality in the hypothalamic-pituitary-gonadal axis at one or more sites. Regardless of the site(s) or dysfunction, we postulate that excessive androgen production is a major factor contributing to menstrual irregularities. Androgen imprinting, which may lead to permanent impairment of cyclic gonadotropin secretion in female rats (15), has not been shown to occur in primates (16, 17). Many patients with CAH have regular menses and are fertile after neonatal exposure to increased androgen concentrations (3, 18). Earlier studies have shown that the normal pattern of augmented FSH secretion after LRF as well as the normal LH response are present in patients with CAH (19), indicating that pituitary secretion of gonadotropins is not permanently impaired by an excess of androgen in the neonatal period. However, elevated circulating androgen concentrations may modify the responsiveness of the gonadotropes to LRF (20) and block the positive feedback effect of estrogen to prevent cyclic LH secretory surges.

Androgens can have a direct effect on the maturation of ovarian follicles. Louvet *et al.* (21) demonstrated in the rat that androgens cause excess and accelerated atresia of preantral follicles. The exact mechanism of this action is uncertain, but it may involve binding of testosterone to an ovarian protein that has characteristics of a specific androgen receptor (22). These findings suggest the possibility that the circulating androgens in patients with CAH may act locally within the ovary to pre-

vent the maturation of follicles and subsequent ovulation. An additional but less likely possibility is that androgens modify the proliferative or secretory changes in the endometrium to such an extent that menses do not occur. Hence, both a local deleterious effect of excess circulating androgen on the ovary and a central suppressive effect on the pituitary and hypothalamus may have been operative in our patients.

An analogy can be drawn between the menstrual irregularities of patients with 21-hydroxylase deficiency and those with the polycystic ovary syndrome. In both conditions, concentrations of testosterone are often increased. Adolescent and adult female patients with virilizing CAH, before they have received glucocorticoid treatment, may have ovarian histologies similar to those in patients with polycystic ovaries (23). Treatment with glucocorticoids is followed by the return of cyclic menses (24) in some patients with the polycystic ovary syndrome.

Data from the patients in the present study indicate that ACTH and adrenal steroid secretion may not be suppressed throughout an entire 24-h period even when the dose of glucocorticoid is adequate to suppress 17-ketosteroids into the normal range. Moreover, concentrations of plasma ACTH, 17-OHP, and testosterone may not reflect the same pattern of suppression throughout the day. The reason for the variable pattern of ACTH and steroid suppression by glucocorticoids is not clear.

More consistent suppression with a longer acting glucocorticoid led to cyclic menses in four patients who had been amenorrheic or oligomenorrheic. Not all benefit from such a modification of glucocorticoid therapy. Patient 4, the one who remained amenorrheic for a prolonged time interval after high dose glucocorticoids, differed from the others in that she consistently had a normal concentration of plasma testosterone. Clearly, increased levels of testosterone are not the only cause of amenorrhea in patients with CAH.

The present observations suggest that a decrease in plasma testosterone will establish menses or make them more regular in most patients with CAH whose only symptom of androgen excess may be amenorrhea or irregular menses. An optimal treatment program for children with virilizing CAH is one which suppresses androgenic effects yet allows normal growth without undue advancement of bone age. In older female patients who have reached their ultimate height but who have menstrual disorders on conventional glucocorticoid replacement regimens, it is desirable to achieve more continuous adrenal androgen suppression with glucocorticoid preparations in dosages that, while not causing a Cushingoid appearance, frequently may be detrimental to growth in younger children. Such a treatment program may reduce the prevalence of menstrual abnormalities in young women with CAH.

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