0021-972X/95/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 80, No. 2
Printed in U.S.A.

The Impact of Estrogen on Adrenal Androgen Sensitivity and Secretion in Polycystic Ovary Syndrome

EDWARD C. DITKOFF, FRANCA FRUZZETTI, LILLY CHANG, FRANK Z. STANCYZK, AND ROGERIO A. LOBO

Department of Obstetrics and Gynecology, Columbia-Presbyterian Medical Center (E.C.D.), New York, New York 10032; the Department of Obstetrics and Gynecology, University of Pisa (F.F.), Pisa, Italy; and the Department of Obstetrics and Gynecology, University of Southern California School of Medicine (L.C., F.Z.S., R.A.L.), Los Angeles, California 90033

ABSTRACT

Adrenal hyperandrogenism is a common feature of patients with polycystic ovary syndrome (PCO). This may be due to enhanced adrenal sensitivity to ACTH. Because enhanced ovarian androgen secretion does not appear to explain this phenomenon, we explored the role of estrogen in inducing enhanced adrenal sensitivity, in that a state of relative hyperestrogenism exists in PCO.

Eight patients with PCO and seven matched controls received ovine corticotropin-releasing hormone (oCRH; 0.1 μg/kg) iv before and after hypoestrogenism was induced by leuprolide acetate (LA; 1 mg, sc, each day). In patients with PCO, a third oCRH test was repeated after transdermal estradiol (E_2; 0.1 mg) had been applied for a week, during which time LA was continued. At baseline, patients with PCO had increased responses of 11β-hydroxyandrostenedione and dehydroepiandrosterone ($P < 0.03$ and $P < 0.02$) and increased Δ maximal ratios of androstenedione (A4)/ACTH and dehydroepiandrosterone/ACTH ($P < 0.01$) after oCRH treatment. After LA administration to patients with PCO, these ratios were significantly suppressed ($P < 0.01$) and returned to baseline after E_2 was added. There were no changes in controls. Steroid ratio responses to oCRH suggested that 17,20-desmolase activity (Δ maximum change in the ratio of A4/17-hydroxyprogesterone) was lowered with estrogen suppression and increased again after transdermal E_2 administration. There was a significant positive correlation between changes in E_2 levels and Δ maximum change in the ratios of A4/17-OHP after oCRH treatment, signifying 17,20-desmolase activity ($r = 0.58$, $P < 0.02$). In conclusion, these data provide evidence that estrogen is at least one factor that influences adrenal androgen sensitivity in PCO and may help explain the frequent finding of adrenal hyperandrogenism in this syndrome. (*J Clin Endocrinol Metab* **80:** 603–607, 1995)

IT HAS BEEN established that many women with polycystic ovary syndrome (PCO) have increased adrenal androgen secretion (1). Recently, we determined prospectively that in PCO, the prevalence of increased levels of the serum adrenal androgens, dehydroepiandrosterone sulfate (DHEAS) and 11β-hydroxyandrostenedione (11β-OHA), is approximately 60% and that this prevalence is similar among different ethnic groups (2). The adrenal androgen response to stimulation by either ACTH or CRH has been shown to be exaggerated (3–8) or unaffected (9, 10) in the absence of detectable adrenal enzymatic deficiencies.

The ovary has been postulated as having a role or contributing to this adrenal abnormality, but this relationship has never been established. Exogenous androgen has been shown to alter adrenal enzymatic activity to a small degree both *in vitro* and *in vivo* (8, 11–14). However, the role of ovarian androgens in causing the increased adrenal androgen secretion that occurs in PCO has not been established.

On the other hand, we and others have proposed that a relative hyperestrogenic state exists in PCO (15, 16) and that this, in turn, may lead to increased LH secretion in some patients. Recently, it was proposed that a dysregulation of ovarian and adrenal cytochrome P450 17α-hydroxylase/17,20-desmolase activity may occur in PCO (17). Because estrogen is known to influence 17,20-desmolase activity (18, 19), we postulated that the chronic hyperestrogenism of this syndrome, rather than increased ovarian androgen production, might be implicated in the enhanced adrenal androgen sensitivity in PCO. Accordingly, we designed a study to test this hypothesis.

Received May 4, 1994. Revision received September 15, 1994. Accepted October 20, 1994.

Address all correspondence and requests for reprints to: Rogerio A. Lobo, M.D., Department of Obstetrics and Gynecology, Women's Hospital, Room 1M2, 1240 North Mission Road, Los Angeles, California 90033.

Subjects and Methods

Subjects

The study group consisted of eight patients with PCO, aged 25–35 yr, and seven matched normal ovulatory controls, aged 22–35 yr. The first eight PCO patients were recruited and later matched to controls on the basis of age, weight, and height. Subjects with PCO were patients with this diagnosis seen in our Reproductive Endocrinology and Infertility Clinic in Women's Hospital at the Los Angeles County-University of Southern California Medical Center at the time of this study. No subjects were receiving medications or hormonal preparations, and all subjects had perimenarchial onset of chronic anovulation with irregular menses as well as elevated androgen levels, specifically an elevation of DHEAS (>7.30 μmol/L). PRL levels were normal. No patient was virilized, and none had evidence of known adrenal enzymatic deficiencies. All patients had normal basal levels of 17-hydroxyprogesterone (17-OHP; <8000 pmol/L). Patients were mildly hirsute, but Ferriman-Gallwey scores were not evaluated because this was not an entry criterion.

This study was approved by our Institutional Review Board, and written informed consent was obtained from each subject.

Protocol

Normal ovulatory subjects were studied during their midfollicular phases (days 7–10), whereas PCO subjects were studied on the fourth

day of menses, which were induced by an im injection of 150 mg progesterone in oil. The midfollicular phase of controls was chosen because of our previous data demonstrating that the estrogen status of normal women is comparable to that of patients with PCO at this time (20). Both groups received an iv bolus of ovine CRH (oCRH; 0.1 μg/kg) at 1000 h after baseline blood samples were obtained at −15 and 0 min. Further blood samples were collected 15, 30, 60, and 120 min after oCRH. After the oCRH stimulation test, both groups were instructed to self-administer leuprolide acetate (LA; 0.5 mg, sc, twice daily) until estradiol (E_2) levels were less than 105 pmol/L. Serum E_2 was measured after 2 weeks and then weekly until hypoestrogenism was documented. Once E_2 was suppressed, another oCRH stimulation test was carried out, as described above. Normal ovulatory subjects completed the study at this time. Subjects with PCO continued receiving LA after their second oCRH test, but also received an E_2 transdermal patch (Estraderm; 0.1 mg). The E_2 patch was worn on the abdomen and was replaced once every 3.5 days. At the end of 1 week, a third oCRH test was carried out.

Blood samples were placed on ice immediately, and plasma was separated after centrifugation in a refrigerated centrifuge within 1 h. Samples were stored at −70 C until assayed. Serum DHEA, DHEAS, androstenedione (A4), cortisol (F), 11β-OHA, testosterone (T), E_2, 17-OHP, 17α-hydroxypregnenolone (17α-preg), and progesterone (P) were measured by specific RIA (20–23). The ACTH assay used was obtained from ICN Biomedicals (Costa Mesa, CA). All samples from each woman were analyzed in the same assay. The intra- and interassay coefficients of variation did not exceed 6% and 15%, respectively.

Statistical comparisons were made between maximum steroid responses and between maximum steroid ratios, using paired and unpaired *t* tests as well as analysis of variance for multiple group comparisons with *post-hoc* testing. Correlations were calculated by the method of least squares. The results are depicted as the mean ± SE.

Results

Basal values in normal ovulatory subjects and PCO before and after LA treatment are depicted in Table 1. Compared to normal women, PCO subjects had higher baseline levels of T, A4, 11β-OHA, DHEAS, DHEA, and 17-OHP ($P < 0.01$). Serum E_2 and F, and plasma ACTH levels were not different.

In controls, serum T decreased from 1248 ± 243 to 832 ± 104 pmol/mL after LA treatment, but this was only of borderline significance. E_2 levels decreased significantly from 352 ± 40 to 81 ± 11 pmol/L ($P < 0.01$). The other serum androgens, 17-OHP, plasma ACTH, and F were not affected by LA. In PCO subjects, serum T levels decreased from 2774 ± 312 to 1664 ± 138 pmol/L after LA ($P < 0.01$). Serum E_2 levels decreased significantly from 291 ± 62 to 83 ± 7 pmol/L ($P < 0.01$), and serum A4 decreased from 11.2 ± 1.4 to 7.7 ± 0.7 nmoL/L ($P < 0.01$; Table 1).

After the administration of 0.1 mg Estraderm to PCO patients, serum E_2 increased to 440 ± 83 pmol/L, which is not statistically different from the baseline of 291 ± 62. All other hormones remained unaffected (data not depicted). Specifically, the suppressed levels of T and A4 remained unchanged. Free levels of E_2 and sex hormone-binding globulin were not measured during this study.

Figure 1 illustrates maximal (max) androgen responses to oCRH at baseline in both groups of subjects. Serum 11β-OHA values after oCRH in PCO patients (13.3 ± 1.8 nmol/L) were significantly greater than those in controls (8.17 ± 0.9 nmol/L; $P < 0.03$), DHEA levels were also higher (65.7 ± 9.3 *vs.* 38.77 ± 4.8 nmol/L; $P < 0.02$), respectively. The max values of A4 were 18.2 ± 3.1 *vs.* 11.5 ± 1.7 nmol/L and were only of borderline significance.

As a marker of adrenal sensitivity, the Δ max response of androgen compared to the Δ max response of ACTH was expressed as a ratio. Thus, the Δ max responses of A4/ACTH after oCRH treatment and those of DHEA/ACTH were calculated. These ratios at baseline were 5.53 ± 0.6 and 1.65 ± 0.2 in PCO patients, which were greater than these ratios in controls (3.87 ± 0.1 and 0.99 ± 0.2; both $P < 0.05$). In controls, after LA treatment, these ratios did not change significantly and varied by only 2.5 ± 9% and 7 ± 23%, respectively. However, these ratios were altered in PCO. Figure 2 depicts the changes in the Δ max ratios of A4/ACTH and DHEA/ACTH in PCO after LA (low E_2) and then again when E_2 was added. After LA treatment in PCO patients, compared to baseline responses, the Δ max ratio of A4/ACTH after oCRH decreased by 58 ± 10% ($P < 0.01$). The change in the Δ max ratio of DHEA/ACTH also decreased by 33 ± 7% ($P < 0.01$). Baseline values represent the steroid responses to oCRH before LA or after LA plus E_2 treatment. After E_2 was added, these ratios were normalized. The Δ max ratio of A4/ACTH was −8.8 ± 0.5% of baseline values (P = NS), and the ratio of Δ DHEA/ACTH was −2.8 ± 0.4% of baseline (Fig. 2). The suppressed ratios after LA treatment rose statistically after E_2 was added, and this represented a 118 ± 35% change in A4/ACTH ($P = 0.04$) and a 47 ± 25% change in DHEA/ACTH ($P = 0.02$). The changes in the Δ ratios of 11β-OHA/ACTH during these pertubations followed the same trends, but failed to achieve statistical significance (data not depicted).

Ratios of steroid responses after oCRH treatment were used to signify adrenal enzymatic activity. At baseline, Δ max ratios of 17α-preg/17α-prog and of DHEA/A4, which signify 3β-ol-dehydrogenase isomerase activity were similar in PCO and controls. Similarly, Δ max ratios of 17-OHP to F, which signify 21- and 11-hydroxylase activities, were similar in PCO and controls. Ratios of 17-OHP/P were used to

TABLE 1. Mean values before and after leuprolide acetate (LA) treatment in controls and PCO

	Baseline	Controls LA	Baseline	PCO LA
T (pmol/L)	1248 ± 243	832 ± 104	2774 ± 312[a]	1664 ± 138[b]
E_2 (pmol/L)	352 ± 40	81 ± 11[b]	291 ± 62	83 ± 7[b]
A4 (nmol/L)	4.89 ± 1.65	4.19 ± 0.70	11.2 ± 1.4[a]	7.7 ± 0.7[b]
11β-OHA (pmol/L)	38.41 ± 3.84	41.90 ± 5.24	74.02 ± 13.96[a]	63.54 ± 10.47
17-OHP (pmol/L)	726 ± 121	726 ± 121	1997 ± 303[a]	1362 ± 303
DHEAS (μmol/L)	2.72 ± 0.29	3.26 ± 0.41	7.89 ± 0.54[a]	7.35 ± 0.54
DHEA (nmol/L)	12.5 ± 1	13.5 ± 1.4	32.3 ± 5.5[a]	29.6 ± 5.9
ACTH (pmol/L)	9.9 ± 1.0	10 ± 2	13 ± 1.3	12 ± 0.4
F (nmol/L)	248 ± 39	331 ± 36	331 ± 55	331 ± 55

[a] $P < 0.01$, controls *vs.* PCO at baseline.
[b] $P < 0.01$, baseline *vs.* LA in either group.

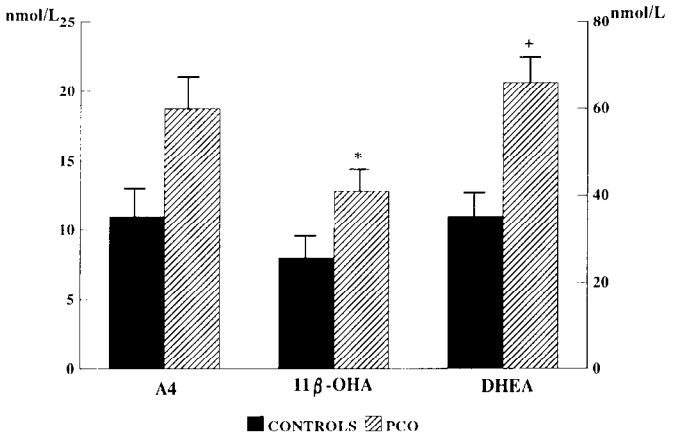

FIG. 1. Baseline responses of A4, 11β-OHA, and DHEA in controls and patients with PCO. The *asterisk* and *cross* indicate significant changes from controls ($P < 0.03$ and $P < 0.02$, respectively).

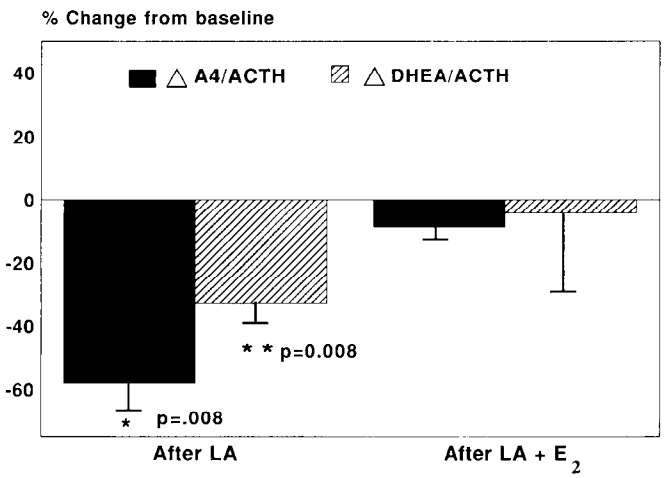

FIG. 2. Percent changes in the Δ maximal A4/ACTH and DHEA/ACTH ratios in response to oCRH after LA and after LA plus E_2 compared to baseline responses in PCO patients. Baseline values represent the steroid responses to oCRH before LA or LA plus E_2. *Asterisks* indicate changes after LA treatment compared to the baseline ($P < 0.01$).

signify 17α-hydroxylase activity, and ratios of A4/17-OHP were used to reflect 17,20-desmolase activity. Although 17α-hydroxylase activity was similar in controls and PCO patients (4.2 ± 0.7 and 3.0 ± 0.8), 17,20-desmolase activity appeared to be higher in PCO patients (4.7 ± 1) compared to controls (3.9 ± 1), although this was not statistically significant.

No changes in these ratios occurred in the controls after LA treatment. For example, the ratio of A4/17-OHP was 3.9 ± 1 before and 3.3 ± 0.7 after LA treatment. For 21- and 11-hydroxylase activities, the ratios were 4.2 ± 0.7 and 4.2 ± 0.5 before and after LA. In PCO, however, significant changes were evident. Although there were no significant changes in the steroid pairs representing 3β-ol-dehydrogenase isomerase or 21- and 11-hydroxylase activities before and after LA treatment (Fig. 3), 17,20-desmolase and 17α-hydroxylase activities were altered. The Δ max ratios of A4/17-OHP decreased from 4.7 ± 1 to 2.2 ± 0.63 ($P = 0.01$) after LA. With

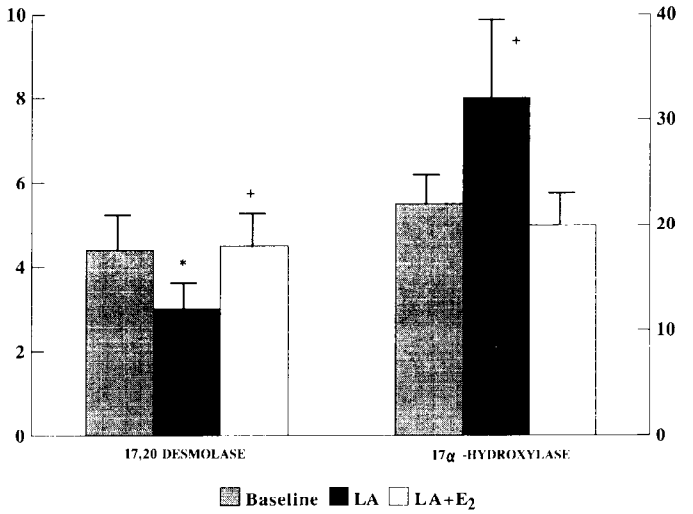

FIG. 3. Steroid ratios, Δ A4/17-OHP and Δ 17-OHP/P, representing 17,20-desmolase and 17α-hydroxylase activities in women with PCO at baseline, after LA, and after LA plus E_2. The *asterisk* and *cross* indicate significant changes compared to the baseline ($P = 0.01$ and $P = 0.02$, respectively). The double cross indicates a significant change when E_2 was added from the LA state.

E_2 added, this ratio increased significantly to 3.9 ± 0.85 ($P = 0.02$). Overall, this ratio (3.9 ± 0.85) was not significantly different from baseline (4.7 ± 1) ($P = 0.24$). The Δ max ratio of 17-OHP/P, which reflects 17α-hydroxylase activity, was also affected. This ratio increased from 3.0 ± 0.8 to 5.17 ± 1.53 ($P = 0.02$) after LA treatment, reflecting the increased levels of 17-OHP that occurred due to reduced conversion to A4 (17,20-desmolase activity) after LA treatment. This ratio decreased again, with the addition of E_2, to 3.2 ± 0.6, but this change was not significant ($P = 0.16$).

The significant changes in 17,20-desmolase activities in PCO before and after estrogen modulation were seen in the Δ^4 pathway, reflected by the ratios of A4 and 17-OHP. The activity in the Δ^5 pathway did not appear to be affected. The Δ max ratio of DHEA/17α-preg was 1.87 ± 0.3 at baseline, 1.74 ± 0.6 after LA treatment, and 1.66 ± 0.4 after the addition of E_2.

Because it appeared that Δ max ratios of A4/17-OHP were influenced by E_2 modulation, we calculated the correlation between serum E_2 and this parameter of 17,20-desmolase activity (Fig. 4). In the eight PCO subjects, a direct positive correlation was found ($P = 0.02$).

Discussion

Although there has been controversy about the prevalence of adrenal androgen excess in PCO, we found that this occurs in up to 60% of patients. Using elevations in the serum markers, DHEAS and 11β-OHA, this was determined prospectively in three separate populations: the United States, Japan, and Italy (2). Earlier studies using ACTH and oCRH in PCO have suggested an enhanced adrenal sensitivity, at least in some women (5–8, 11, 12). Our studies using oCRH showed that in those hyperandrogenic women who were most sensitive to dexamethasone suppression, the ACTH response to oCRH was blunted, but the androgen response

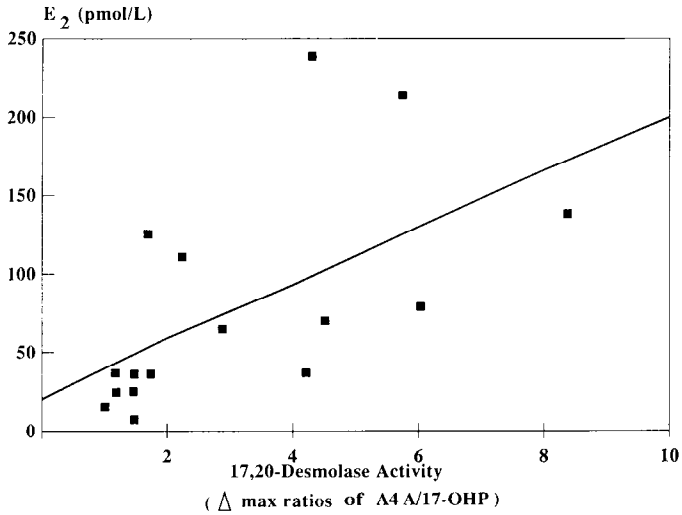

FIG. 4. Correlation between the E_2 level and 17,20-desmolase activity, as represented by the Δ maximal A4/17-OHP ratio after oCRH treatment ($P < 0.02$ and $r = 0.58$).

was increased (5). This finding suggests that a heightened adrenal sensitivity exists in patients with adrenal androgen excess. Our study is different from previous reports (12) in that we specifically selected women who had a predominance of adrenal androgen secretion.

As it was not convincing to us that ovarian androgens could explain this enhanced adrenal sensitivity, we postulated that estrogen might be involved. That estrogen plays a role in stimulating 17,20-desmolase activity has been known for some time (18, 19). We also wished to reexamine the notion that patients with PCO may have dysregulated 17α-hydroxylase and 17,20-desmolase activities (17). In designing our study, therefore, we selected women with PCO who had elevated levels of the adrenal androgen marker, DHEAS. Because of this, our study does not attempt to extrapolate these findings to all patients with PCO. Indeed, there is marked clinical heterogeneity among patients.

In this study, we found that our patients with PCO had enhanced adrenal androgen activity and that this response is influenced by estrogen. The ratios of Δ max changes in androgen to ACTH responses after oCRH were chosen to represent adrenal sensitivity, which was affected by alterations in estrogen status. Statistical changes were found with A4 and DHEA ratios, but not with 11β-OHA. This was surprising, but may have been due to our sample size. Indeed, the trends were similar to the responses of A4 and DHEA.

In PCO, a relative state of hyperestrogenism exists. Elevated unbound E_2 and estrone levels have been demonstrated in the past, which together place the estrogen status of PCO patients around the midfollicular phase of the menstrual cycle. During this state of relative hyperestrogenism, there is no opposition by progesterone, and the condition continues chronically. This estrogen status often leads to abnormal uterine bleeding, which may lead to endometrial disease, but has also been suggested to explain at least in part the gonadotropin abnormalities of most patients. In addition, we suggest that it may enhance adrenal sensitivity.

Although it is difficult to exclude dysregulation of cytochrome P450 in patients with PCO, here we were not able to confirm the dysregulation of adrenal cytochrome P450 17α/17,20-desmolase activity. The steroid ratios after oCRH treatment signifying this and specifically the Δ 17-OHP/P ratio were similar in controls and PCO patients. It is possible that the oCRH stimulus, which results in the release of physiological levels of ACTH, is not sufficient to uncover a subtle abnormality. It is also possible that the dysregulation, if it exists, is expressed primarily in the ovary. Finally, it is equally plausible that not all patients with PCO will exhibit an enzyme dysregulation, in that the syndrome is extremely heterogenous.

Our findings suggest that the estrogen status of women is at least one factor that influences adrenal 17,20-desmolase sensitivity. Although baseline Δ ratios of A4/17-OHP were similar in PCO and controls, the adrenal in PCO was more sensitive to ACTH, and the Δ A4/ACTH ratio was significantly increased. The 17,20-desmolase activity appeared to be the most affected and cause the interpretation of heightened adrenal sensitivity. Δ ratios of A4/17-OHP decreased, whereas the ratio of 17-OHP/P tended to increase. We interpret these reciprocal changes as being due to changes in 17-OHP. A direct positive correlation was found between the E_2 level and the calculated ratios representing 17,20-desmolase activity ($r = 0.58$; $P < 0.02$). These findings in 17,20-desmolase activity were only evident in the Δ^4 pathway, and we found no changes related to DHEA and 17α-preg.

In conclusion, our data suggest that estrogen may be responsible at least in part for some of the adrenal sensitivity observed in hyperandrogenic women with PCO. Clearly, other factors may be involved as well. Further, as it is our contention that virtually all women with PCO have a state of chronic hyperestrogenism, other factors must be involved, which lead to adrenal androgen excess in some women, yet not in others.

References

1. **Hoffman DI, Klove K, Lobo RA.** 1984 The prevalence and significance of elevated dehydroepiandrosterone sulfate levels in anovulatory women. Fertil Steril. 42:76–81.
2. **Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA.** 1992 Does ethnicity influence the prevalence of adrenal hyperandrogenims and insulin resistance in polycystic ovary syndrome? Am J Obstet Gynecol. 167:1807–1812.
3. **Mongioi A, Macchi M, Vicari E, et al.** 1988 Pituitary and adrenal response to ovine corticotropin-releasing hormone in women with polycystic ovarian syndrome. J Endocrinol Invest. 11:637–640.
4. **Lobo RA.** 1984 The role of the adrenal in polycystic ovary syndrome. Semin Reprod Endocrinol. 2:251–262.
5. **Carmina E, Levin JH, Malizia G, Lobo RA.** 1990 Ovine corticotropin-releasing factor and dexamethasone responses in hyperandrogenic women. Fertil Steril. 54:245–250.
6. **Carmina E, Lobo RA.** 1990 Pituitary-adrenal responses to ovine corticotropin-releasing factor in polycystic ovary syndrome and in other hyperandrogenic patients. Gynecol Endocrinol. 4:225–232.
7. **Hague WM, Honour JW, Adams J, Vecsei P, Jacobs HS.** 1989 Steroid responses to ACTH in women with polycystic ovaries. Clin Endocrinol (Oxf). 30:355–365.
8. **Gibson M, Lackritz R, Schiff I, Tulchinsky D.** 1980 Abnormal adrenal responses to adrenocorticotropic hormone in hyperandrogenic women. Fertil Steril. 33:43–48.
9. **Azziz R, Gay FL, Potter SR, Bradley Jr E, Boots LR.** 1991 The effects of prolonged hypertestosteronemia on adrenocortical biosynthesis in oophorectomized women. J Clin Endocrinol Metab. 72:1025–1030.

10. **Futterweit W, Green G, Tarlin N, Dunaif A.** 1992 Chronic high dosage androgen administration to ovulatory women does not alter adrenocortical steroidogenesis. Fertil Steril. 58:124–128.
11. **Vermesh M, Silva PD, Rosen GF, Vijod AG, Lobo RA.** 1988 Effect of androgen on adrenal steroidogenesis in normal women. J Clin Endocrinol Metab. 66:128–130.
12. **Fruzzetti F, Melis GB, Mais V, et al.** 1991 High testosterone levels of ovarian origin affect adrenal steroidogenesis? J Clin Endocrinol Metab. 72:426–431.
13. **Sharma DC, Forchielli E, Dorfman RI.** 1973 Inhibition of enzymatic steroid 11β-hydroxylation by androgens. J Biol Chem. 238: 572–580.
14. **Leventhal ML, Scommegna A.** 1963 Multiglandular aspects of the Stein-Leventhal syndrome. Am J Obstet Gynecol. 87:445–454.
15. **DeVane GW, Czekala NM, Judd HL, Yen SSC.** 1975 Circulating gonadotropins, estrogens, and androgens in polycystic ovarian disease. Am J Obstet Gynecol. 121:496–500.
16. **Lobo RA, Granger L, Goebelsmann U, Mishell Jr DR.** 1981 Elevations in unbound serum estradiol as a possible mechanism for inappropriate gonadotropin secretion in women with PCO. J Clin Endocrinol Metab. 52:156–158.
17. **Rosenfield RL, Barnes RB, Cara JF, Lucky AW.** 1990 Dysregulation of cytochrome P450c17α as the cause of polycystic ovarian syndrome. Fertil Steril. 53:785–791.
18. **Lobo RA, Goebelsmann U, Brenner PF, Mishell Jr DR.** 1982 The effect of estrogen on adrenal androgens in oophorectomized women. Am J Obstet Gynecol. 142:471–478.
19. **Schiebinger R, Albertson B, Cassorla F, et al.** Changes in adrenal enzyme activity associated with human adrenarche. Proc of the 62nd Annual Meet of The Endocrine Soc. 1980. (Abstract 533).
20. **Barnes RB, Mileikowsky GN, Cha KY, Spencer CA, Lobo RA.** 1986 Effects of dopamine and metoclopramide in polycystic ovary syndrome. J Clin Endocrinol Metab. 63:506–509.
21. **Lobo RA, Paul WL, Goebelsmann U.** 1981 Dehydroepiandrosterone sulfate as an indicator of adrenal androgen function. Obstet Gynecol. 57:69–73.
22. **Stanczyk FZ, Chang L, Carmina E, Putz Z, Lobo RA.** 1991 Is 11β-hydroxyandrostenedione a better marker of adrenal androgen excess than dehydroepiandrosterone sulfate? Am J Obstet Gynecol. 165:1837–1842.
23. **Lobo RA, Goebelsmann U.** 1981 Evidence for reduced 3β-ol-hydroxysteroid dehydrogenase activity in some hirsute women thought to have polycystic ovary syndrome. J Clin Endocrinol Metab. 53:394–400.