Endocrine

POLYCYSTIC OVARIAN DISEASE

Department of Internal Medicine

Grand Rounds

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I. PATIENT PROTOCOLS

A. Patient 1 - PCOD with hirsutism

D.A. is a 22 y/o black woman who was seen because of progressive growth of facial and body hair. Facial and truncal hair began at the time of menarche (age 13) and has been gradually worsening ever since. Menses have always been irregular occurring at 1 to 5 month intervals. She has never been pregnant. She plucks chin whiskers once a week but does not remove mustache hairs or prominent temporal sideburns. The family history is negative for similarly affected women, and she takes no medications. On physical exam she was noted to weigh 143 pounds and to have pronounced hirsutism including the facial hair described above, periareolar hair, and a pronounced male escutcheon. Pelvic exam was remarkable for vaginal and cervical mucus typical of an estrogen effect and a 5-6 cm right adnexal mass. The right ovary could not be palpated distinct from the mass, and the left ovary was not palpable. Laboratory exam: plasma testosterone 1.0 ng/ml (nl < 0.6), plasma androstenedione 4.0 ng/ml (nl < 3.0), plasma LH 25 mIU/ml (nl follicular phase 5-15), plasma FSH 4 mIU/ml (nl 5-15), urinary 17-ketosteroids 10.3 mg/24 h (nl 5-15). Because of the adnexal mass an exploratory laparotomy was performed disclosing chronic pelvic inflammatory disease leading to right hydrosalpinx. The right ovary was enlarged, but the left was normal in size. Both ovaries were polycystic. A right salpingo-oophorectomy and a 30% wedge resection of the left ovary was performed. Postoperatively the plasma testosterone was 0.5 ng/ml and the plasma androstenedione 2.0 ng/ml. She was subsequently lost to followup.

B. Patient 2 - Ovarian hyperthecosis with amenorrhea and virilization

D.S. is a 26 y/o white woman who was seen complaining of amenorrhea for 9 years. She had also noted excessive growth of body hair, beard growth (for which she shaves daily), recession of the temporal hairline, and deepening of the voice for approximately 8 months. Menarche occurred at 13 years of age. Menstruation occurred at regular monthly intervals until age 17 when menses ceased abruptly at approximately the time of her mother's death. She had never been pregnant. She denied a family history of excess hair growth or amenorrhea. On physical exam she was noted to weigh 158 pounds, have a B/P of 155/105, and to be a muscular-appearing woman with a loss of female body contours, healed acne, temporal recession of the hairline, and a moderate degree of beard growth. Fundoscopic exam revealed arteriolar narrowing. Cardiac exam was normal. The abdomen was scaphoid, and there were no striae. On pelvic exam there was male escutcheon and slight clitoromegaly. The ovaries were not palpable because of voluntary guarding. The remainder of the physical exam revealed excess body hair on the trunk and extremities but was otherwise unremarkable. Urine metanephrine and hypertensive intravenous pyelogram were normal. Urinary 17-ketosteroids were 24.2 mg/24 h and urinary 17-hydroxycorticoids were 13.5 mg/24 h (nl 4-13). Plasma hormone levels: testosterone 3.6 ng/ml, androstenedione 4.9 ng/ml, LH 22.4 mIU/ml, FSH 4.2 mIU/ml. At laparotomy she was found to have bilateral ovarian hyperthecosis. A bilateral wedge resection was performed. Postoperatively her plasma hormone measurements were: testosterone 0.8 ng/ml, androstenedione 3.0 ng/ml, LH 12.7 mIU/ml, FSH 11.2 mIU/ml. The reduction in the plasma testosterone concentration following ovarian wedge resection was accompanied by a subjective reduction in the degree of hirsutism. In the fifth postoperative month she had a biphasic temperature pattern followed by menstruation. In subsequent cycles a luteal phase plasma progesterone concentration greater than 5.0 ng/ml suggested that ovulation had occurred.

C. Patient 3 - PCOD with oligomenorrhea

Z.C. is a 19 y/o white woman who was seen for oligomenorrhea. She had never been pregnant and her last menstrual period was two and one-half months prior to evaluation. Menarche occurred at the age of 12 and since then menses had been occurring irregularly at 1 to 2 month intervals. The menses were typically painless and not associated with premenstrual symptoms. She was single and did not desire fertility. In the last year she had consulted a dermatologist for acne. The remainder of the history was unremarkable. On physical exam she weighed 118 pounds, had a male escutcheon, no clitoromegaly, abundant cervical mucus and normal-sized ovaries. A basal body temperature profile was biphasic during one cycle and menses followed 12 days after the temperature shift, but the next cycle was monophasic until day 24. Plasma hormone levels: testosterone 1.7 ng/ml, androstenedione 2.3 ng/ml, LH 22 mIU/ml, FSH 10 mIU/ml. She was given oral contraceptives and had regular withdrawal bleeding.

D. Patient 4 - PCOD with infertility

D.K. is a 21 y/o married woman who had failed to conceive after more than a year of unprotected intercourse and was seen for primary infertility. Menarche had occurred at age 17 which was characteristic for women in her family. Her last menstrual period was three and one half months prior to evaluation. She had a normal pelvic exam with cervical mucus characteristic of an estrogen effect. The ovaries were not enlarged. The administration of Provera 10 mg p.o. daily for 5 days resulted in withdrawal bleeding. Plasma hormone levels: testosterone 1.0 ng/ml, LH 28 mIU/ml, FSH 12 mIU/ml. Clomid 50 mg p.o. daily was given on day 5 to 9 of the cycle that was initiated by the Provera. On day 21 the basal body temperature increased and on day 48 a urine pregnancy test was positive.

II. NORMAL OVARIAN FUNCTION

An understanding of the pathophysiology of PCOD requires some consideration of normal ovarian function and its control by the hypothalamic-pituitary system. Studies in the last several years have extended to the human ovary in vitro assessment of the various compartments detailing hormone receptors, steroid production, and even hormone concentrations in the microenvironment of the ovarian follicle (1-5).

A. Follicle Development

The fundamental reproductive unit of the ovary is the primordial follicle. It consists of an oocyte, a single layer of granulosa cells, and a basement membrane that separates the follicle from the surrounding interstitial tissue. At various times throughout the menstrual cycle a small percentage of the primordial follicles begin to grow apparently independent of pituitary gonadotropins. When the granulosa cells begin to divide and take on a cuboidal shape the follicle is termed a primary follicle. As the primary follicle matures three types of changes occur: (1) FSH, androgen, and estrogen receptors appear in the granulosa cells; (2) gap junctions develop between adjacent granulosa cells and between granulosa cells and the oocyte; and (3) the theca interna develops as an outer surrounding layer consisting of a capillary network with clusters of steroid-secreting cells.

The primary follicle becomes a secondary follicle with the appearance of an antrum or fluid-filled cavity. One of these secondary follicles is somehow selected on day 1 of the menstrual cycle to grow and eventually differentiate into the

preovulatory follicle. During this two-week period of maturation three types of changes occur in the follicle: (1) LH, prolactin, and prostaglandin receptors either first appear or increase in number; (2) the aromatase enzyme complex that converts androgen to estrogen is induced; and (3) there is formation of follicular fluid with an increasing concentration of estradiol (1-2 μg/ml in the preovulatory follicle). Even before the preovulatory can be morphologically distinguished from the other secondary follicles destined for atresia, on day 7 of the cycle the estradiol concentration is greater in the ovarian vein from the side that contains the preovulatory follicle. Evidence suggests that both the theca interna and the granulosa cells are required for normal estrogen formation and that both LH and FSH are required (Figure 1). FSH induces the aromatase enzyme complex in granulosa cells as well as the appearance of LH receptors on the theca interna cells. The theca interna cells respond to LH by synthesizing primarily androgens which then diffuse across the basement membrane into the granulosa cells where, in response to FSH, they are aromatized to estrogen. In light of the high concentration of estradiol in normal follicular fluid, this FSH-induced aromatization capacity may be critical for follicular development (5).

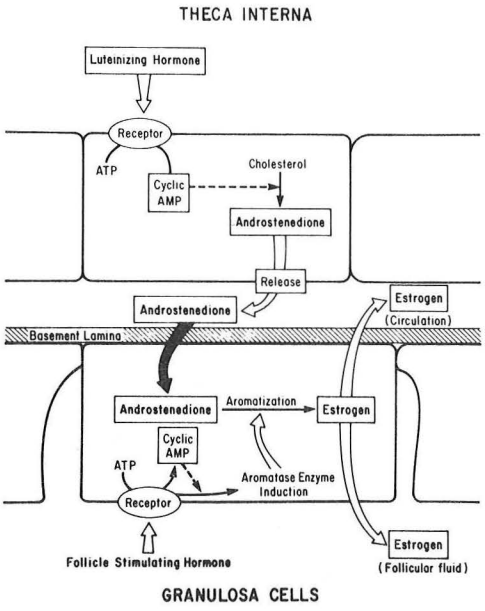

Figure 1

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B. Ovulation

The complex interaction of the hypothalamus, pituitary and ovary required for normal cyclic ovarian function is still incompletely understood (6-10). The well known pattern of plasma hormone concentrations during the normal menstrual cycle are reproduced in Figure 2 for reference. During the second half of the follicular phase (7-8 days prior to the LH surge) there is a gradual increase in plasma estradiol levels as a result of ovarian secretion. (Plasma estrone levels increase as well but not to the same extent since only about one-third of the estrone produced comes from direct secretion.) In some way the rising plasma estradiol level initially results in a gradual increase in LH secretion by the pituitary until estradiol reaches a level at which it exerts a positive feedback effect on the hypothalamus and pituitary causing the midcycle surge in release of FSH and LH. Apparently a presistent high concentration of estradiol coupled with effects of catecholamines and prostaglandins influence the secretion of the hypothalamic peptide LHRH and the response of the pituitary gonadotropes to LHRH. LHRH secretion appears to be regulated by a dual catecholaminergic system in which dopamine exerts inhibitory effects and norepinephrine facilitatory effects on release. There seems to be less endogenous dopamine inhibition of LHRH-release during the preovulatory phase (8).

In response to LH-FSH stimulation cells in the ovarian surface epithelium enlarge and become filled with vesicles containing proteolytic enzymes. About 24 hours after the LH surge these cells degenerate and release their proteases; the resultant tissue degradation facilitates expulsion of the oocyte into the peritoneal cavity.

For the discussion of PCOD the important event to remember is that normal ovulation requires an appropriate rise in estradiol for a sufficient length of time.

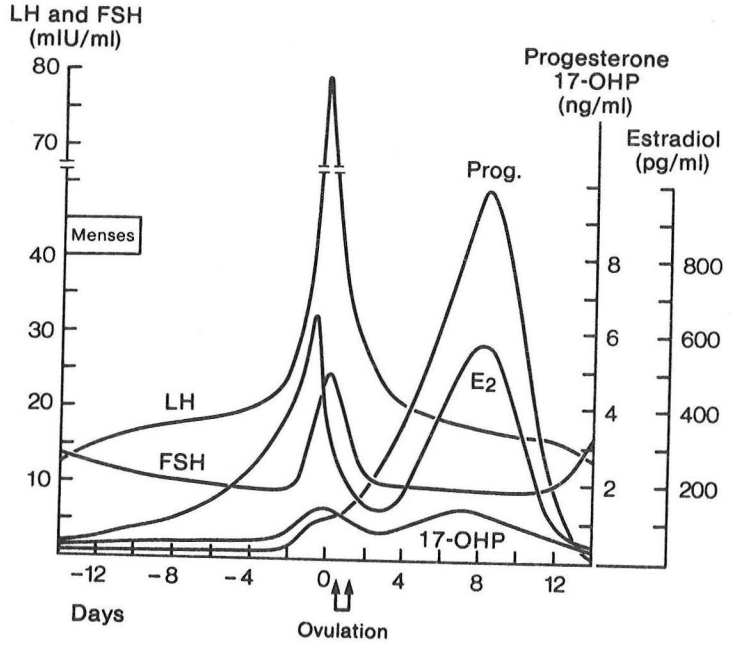

Figure 2

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III. ANDROGENS IN WOMEN

A. Sources, Types, Transport, Metabolism

In contrast to estrogen production, which in normal premenopausal women is primarily via direct secretion of estradiol by the ovary, normal androgen production is dependent on ovarian and adrenal function (11-17). Although there are a number of steroid hormones in women with some androgenic potency (e.g., dehydroepiandrosterone or DHEA, androstenedione, dihydrotestosterone, Δ^5-androstenediol, and 3α-androstanediol), the primary physiologically active androgen in both normal and virilized women is testosterone (Figure 3). The androgenic potency of dehydroepiandrosterone, androstenediol, and androstenedione resides in their capacity to be converted to testosterone (Figure 3). Circulating testosterone in turn either acts directly or following its metabolism to dihydrotestosterone and androstanediol in target tissues.

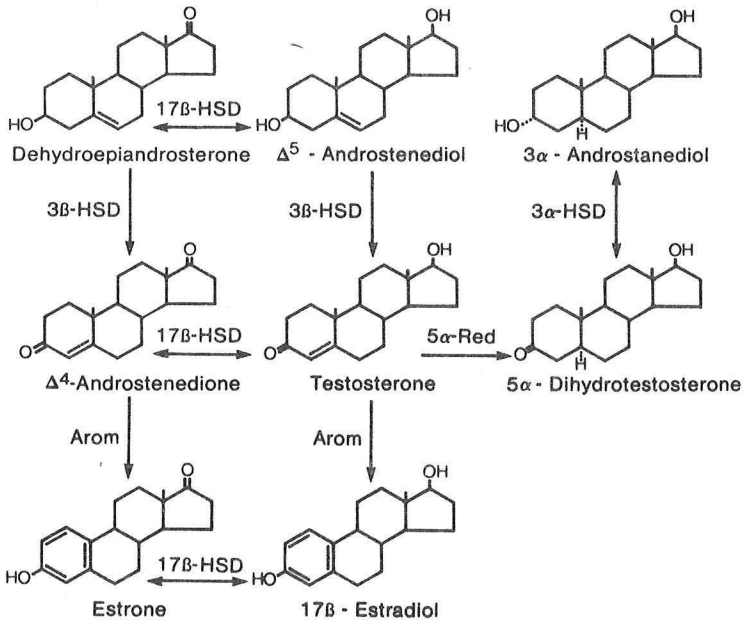

Figure 3

Plasma testosterone levels in women are a function of production by direct secretion from the ovary (25%), direct secretion from the adrenal (25%), and peripheral conversion of precursors secreted from both the ovary and the adrenal (50%), and finally clearance by the liver and extrahepatic tissues (Figure 4). The principal precursor of plasma testosterone secreted by both the ovary and adrenal is androstenedione (13). DHEA and Δ^5-androstenediol combined probably account for less than 10% of testosterone production in normal women (15). The relative contribution of the ovary varies somewhat during the menstrual with a relatively greater contribution of the ovary during the mid portion of the cycle (18, 19). Although the liver is the primary site of testosterone clearance, an increase in extrahepatic clearance, primarily in tissues such as skin and hair follicles, is observed in states of elevated testosterone production.

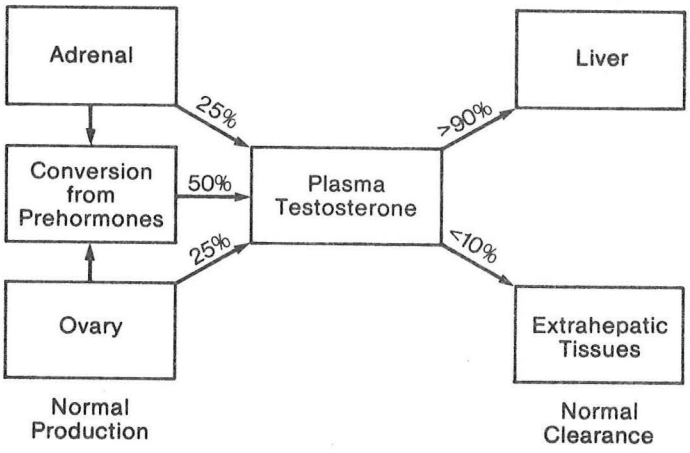

Figure 4

As in men, 97-99% of the total circulating testosterone in women is bound to testosterone binding globulin (TeBG) and albumin (20, 21). The TeBG binding capacity in an apparent determinant of the metabolic clearance (MCR) of testosterone and other steroid, i.e., steroids which have high amount of binding to TeBG have a lower MCR (Table I). (The MCR is defined as the volume of blood completely cleared of the steroid per unit time.) Although the TeBG-bound androgens are not available for metabolic transformation in the peripheral tissues, the albumin-bound fraction is available for such reactions. In the case of testosterone the MCR has been shown to be related to the amount of free plus the amount of albumin-bound hormone (17). The production rate of a steroid equals the product of the plasma concentration and the MCR.

Table I. Plasma concentration (PC), MCR, production rate (PR), and relative binding to TeBG and potency of several androgens in women

Steroid	PC ng/ml	MCR L/24 h	PR mg/day	TeBG binding	Relative Potency
Testosterone	< 0.6	690	0.25	100	100
Androstenedione	< 3.0	2010	3.00	4	15
DHEA	4.0	1500	6.00	2	5
Dihydrotestosterone	0.2	400	0.08	290	200
Δ^5-Androstenediol	0.9	580	0.53	100	12
3α-Androstanediol	0.02	1021	0.02	50	50

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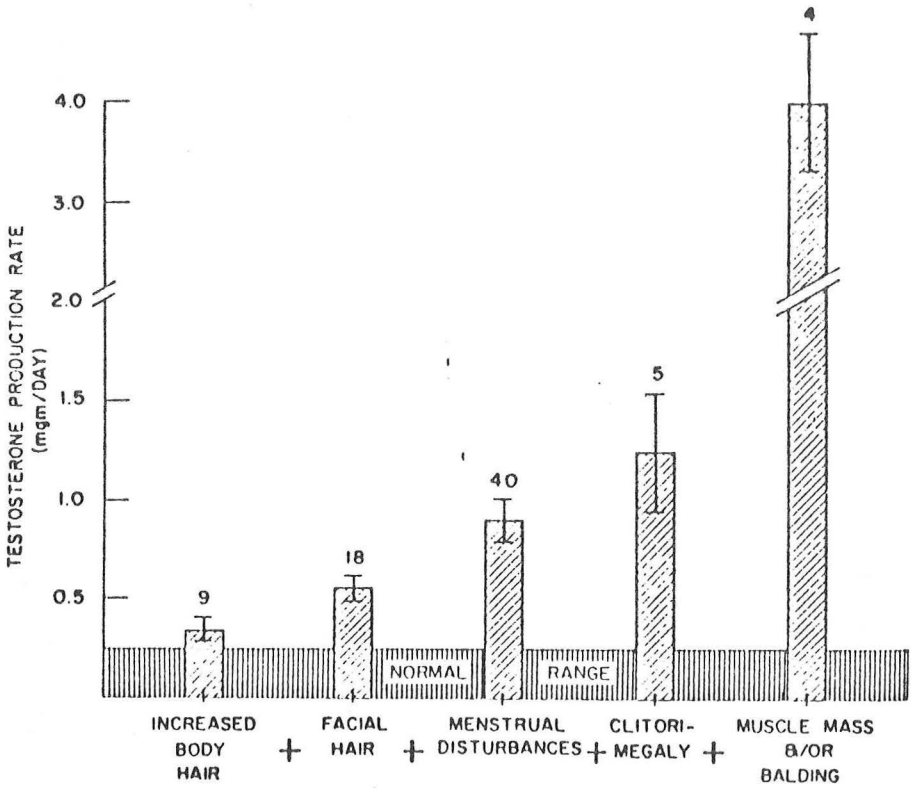
B. Effects of Excess Androgen and Their Assessment

The physiological role of androgens in women is not clear but in excess quantities androgens cause hirsutism, defeminization, and virilization (22-24). The earliest sign of androgen excess is usually increased growth of body and facial hair (24). Consideration of the wide variability of hair growth among normal individuals must be taken into account in the evaluation of any single patient. Such variability is due to endocrine, genetic, and other undefined factors that influence growth of hair. Axillary and lower pubic hair growth, dependent on adrenal androgen, is the same in men and women. The upper pubic, facial, ear, extremity, and truncal hair in men is dependent on testicular androgens (primarily testosterone). Scalp hair growth in the frontal and occipital regions is inhibited by testicular androgen in some individuals. Dark-haired, darkly-pigmented whites of either sex tend to be more hirsute than blonde or fair-skinned persons. Orientals, American Indians, and blacks are less hirsute than whites. There is also considerable variation of hair patterns within family groups.

Hirsutism, defined as the growth of hair in women in a pattern characteristic of men, is a common complaint. Although semiquantitative criteria have been established to help define increased hair growth, it is the subjective interpretation of the patient of an increase in body hair that prompts her to seek medical attention. The critical issue in any such patient is to assess the history of the hirsutism, to decide whether the hair growth is outside the range of normal, and to evaluate for any evidence of frank virilization -- clitoromegaly, increased laryngeal size with deepening of the voice, occipital or frontal balding, and/or increased muscle mass. Hirsutism and clitoromegaly are the most frequent signs of virilization in patients with androgen overproduction. Clitoromegaly may be assessed by calculation of the clitoral index, the product of the length and width of the clitoris in square millimeters. In assessing size, the prepuce of the clitoris should be retracted so that the size of the glans can be appreciated. Ninety-five percent of normal women have a clitoral index less than 35 mm^2(25). Voice changes, balding, and increased muscle mass are late signs of a severe virilizing process. When virilization is severe it is usually accompanied by signs of defeminization including not only amenorrhea but also a decrease in breast size and loss of female body contours.

Studies of testosterone production rates in a large number of women with hirsutism and virilization demonstrate a correlation of increasing testosterone production with severity of virilization (Figure 5). However, significant androgen overproduction may be present with only minimal signs of virilization (perhaps reflecting a short duration of the virilizing process).



Testosterone production rates (± SE) in women with progressive manifestation of virilization. The number of patients examined in each category is noted above the respective bar.

Figure 5

Measurement of testosterone production rates is a research procedure, and the clinician usually must rely on plasma levels as indication of testosterone excess. However, two effects of increased testosterone production make interpretation of plasma testosterone levels difficult. First, as discussed above, increased testosterone production is associated with an increased extrahepatic clearance (e.g., the MCR of testosterone in men is about twice that in women). Thus an increased testosterone production may be present with little or no increase in the plasma concentration (14). The second effect of increased testosterone production is suppression of hepatic synthesis of TeBG. Since most asays of plasma testosterone measure total circulating hormone, a depressed level of TeBG may mask an increase in free testosterone concentration (26-28). Thus direct measurement of free testosterone concentration or TeBG may be helpful in interpreting "high normal" total plasma testosterone levels in women suspected of having increased testosterone production (Figure 6). Free testosterone levels are available through Endocrine Sciences and TeBG levels can be obtained at Baylor.

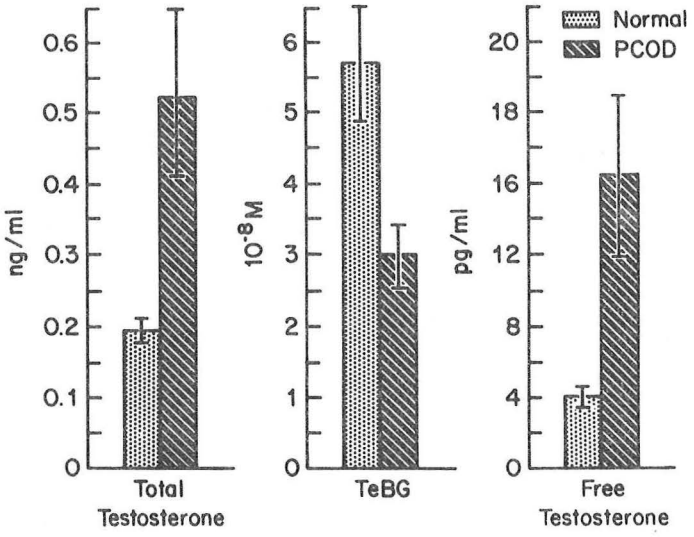


Figure 6

The mean total testosterone of the patients in this figure though higher than the mean of controls is not above the usual upper limit of normal (0.6 ng/ml). Associated with almost a 50% decrease in TeBG concentration the free testosterone concentration in the patients is four times the level found in controls. One must remember that other conditions affect TeBG production. Administration of progestagens, glucocorticoid excess, and hypothyroidism are also associated with decreased levels of TeBG. Thyroid hormone excess and administration of estrogens increase TeBG concentrations.

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IV. THE CLINICAL SYNDROME

A. Clinical Manifestations

Polycystic ovarian disease (PCOD) is the term now applied to the syndrome originally described by Stein and Leventhal in 1935 (29) characterized by enlarged cystic ovaries, obesity, amenorrhea, and hirsutism. Since these features are not uniformly present in all patients with the same endocrine pathophysiology (Table II), the less restrictive term PCOD is preferable (30-32). The seemingly distinct histological entity of ovarian hyperthecosis (33) (in which there are isolated luteinized theca-like cells in the stroma) is probably just one extreme in the spectrum of PCOD (34).

Table II. Signs and Symptoms Associated with Polycystic Ovarian Disease

Symptom or Sign	No. Usable Cases	Frequency (%)	
		Mean	Range
Infertility	596	74	35-94
Hirsutism	819	69	17-83
Amenorrhea	640	51	15-77
Obesity	600	41	16-49
Dysfunctional Bleeding	547	29	6-65
Virilization	431	21	0-28

Based on 1079 cases (Goldzieher and Axelrod)

The hallmark of the disease is chronic anovulation as manifested by infertility, oligo- or amenorrhea, and dysfunctional uterine bleeding. About half the patients are obese. The majority have hirsutism but less than a fifth are virilized. In about half of patients the ovaries are palpably enlarged. It is important to recognize however that PCOD may occur in women who are not obese, do not have amenorrhea or hirsutism, and do not have palpably enlarged ovaries. Histologically the ovaries are usually chracterized by increased surface collagenization, multiple follicular cysts, and numerous atretic cysts lined by hyperplastic theca cells. The ovarian stroma is also usually hyperplastic.

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B. Inheritance and Chromosomal Studies

A positive family history for hirsutism does not necessarily mean that the hirsutism is not pathological. Careful studies of relatives of patients with PCOD indicate that the disorder may be transmitted in an autosomal dominant pattern (Figures 7 and 8) (35-39).

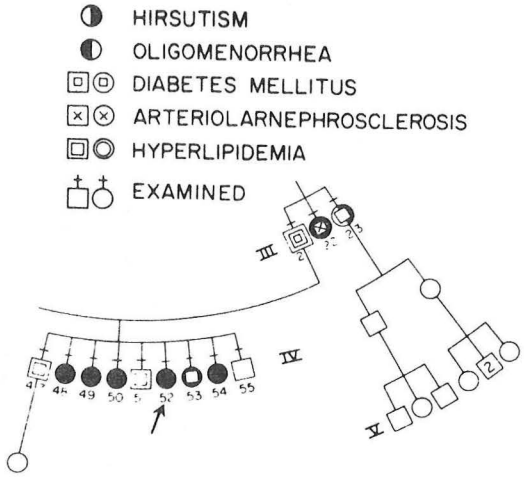

Fig. 7. Partial pedigree of *Family I* illustrating hirsutism and oligomenorrhea in the proband, *IV-52*, and her 5 sisters.

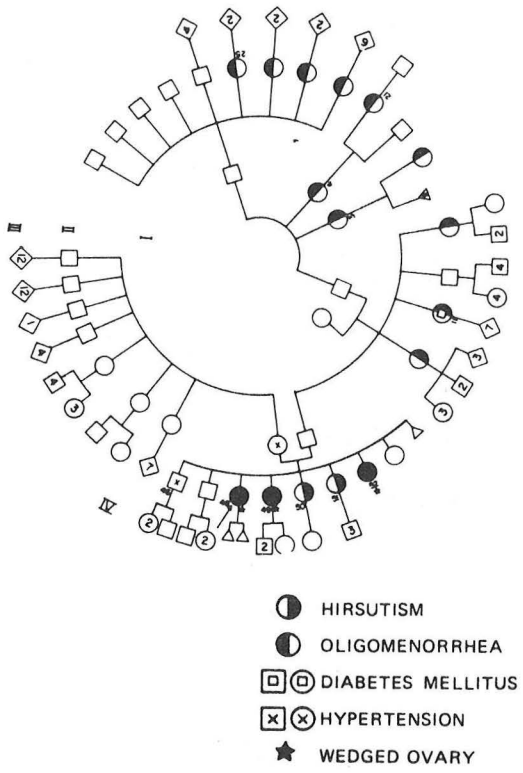

Fig. 8. Pedigree of *Family II* in which 3 sisters, *III-48*, *III-49*, and *III-52*, have polycystic ovarian disease with hyperthecosis, hirsutism and oligomenorrhea.

Givens and coworkers studied the incidence of oligomenorrhea and/or hirsutism in 48 sibships of 18 families in which one or more members of each family had histologically proven PCOD (Table III) (34, 36).

Table III. Sibship studies of patients with oligomenorrhea and/or hirsutism

Relatives Affected:	Maternal Only	Paternal Only	Maternal and Paternal
No. of Sibships	28	15	5
Affected Members	39	41	9
Total Members	93	47	10
Percentage Affected	42%	87%	90%

If this two-fold enhancement of the incidence of affected members in the paternal transmission sibships is real, an X-linked dominant mode of inheritance is a possibility (although autosomal dominant inheritance cannot be excluded). In support of X-chromosome abnormality in some patients are the reports of deletions and mosaicism of the X-chromosome and occasional association of Turner features (reviewed in Ref. 40). However, most women with PCOD have a normal 46,XX chromosomal complement (41).

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C. Endocrinology

The endocrinology of PCOD is the subject of continued investigation (13-15, 24, 26-28, 42-49, reviewed in 50). The rates of production of a number of androgens have been shown to be increased in PCOD. All patients have increased production rates of testosterone and its principal precursor androstenedione (13-15) and most have increased production of DHEA and Δ^5-androstenediol as well (15). On average plasma levels of testosterone, androstenedione, DHEA, DHEA-sulfate (DHEA-S), and 17-hydroxyprogesterone are increased in patients with PCOD (Figure 9), but there is considerable overlap of individual values with normals (44). [The overlap of plasma androgen levels with normals is probably due to the known depressed levels of TeBG (42) and the failure to measure free levels (27, 28) discussed above.] The glandular source of the increased androgens is still somewhat controversial, but at least for testosterone and androstenedione evidence suggests that the ovaries are the primary source (24, 51-54). Since catheterization studies suggest that dexamethasone may suppress androgen levels in patients with primarily ovarian hypersecretion (24), classic endocrine manipulations to differentiate adrenal from gonadal sources (e.g., glucocorticoid administration) must be interpreted with caution. However, as shown in Figure 9, even with 4 mg of dexamethasone a day, mean plasma testosterone and androstenedione levels do not decrease to normal in patients with PCOD in contrast to the suppression of DHEA or DHEA-S suggesting an ovarian origin. Using retrograde venous catheterization and selective sampling of ovarian and adrenal androgens, Kirschner and his colleagues found the ovaries to be the principal source of testosterone and androstenedione in PCOD (24, 52, 54). These same studies seemed to support the dexamethasone suppression data with evidence of significant gradients of DHEA and DHEA-S in the adrenal vein specimens. 17-Hydroxyprogesterone and Δ^5-androstenediol seemed to have a combined adrenal and ovarian source while no gradient for dihydrotestosterone could be demonstrated suggesting that it is primarily formed in the periphery. Thus the data suggest a combined adrenal and ovarian source of androgen excess in PCOD but that the ovary is the major source of the excess testosterone and of its major precursor androstenedione.

Estrogen levels and their sources in PCOD differ significantly from those in normal women (44, 46, 49). Estradiol levels are typically in the low follicular phase range whereas estrone levels are high -- in the range characteristically seen during the preovulatory phase of a normal menstrual cycle. The source of this elevated estrone production is extraglandular aromatization of ovarian-derived androstenedione (44, 49).

Gonadotropin levels are seemingly inappropriate in PCOD (43, 46). LH levels are elevated and LH secretion is with an exaggeration of the normal pulsatile discharge in spite of high circulating levels of androgens and estrogens (Figure 10). FSH levels in contrast are relatively low (Figure 10) and result in abnormal high LH to FSH ratio (usually greater than 2). Neither LH nor FSH exhibits a cyclic surge typical of the usual menstrual cycle.

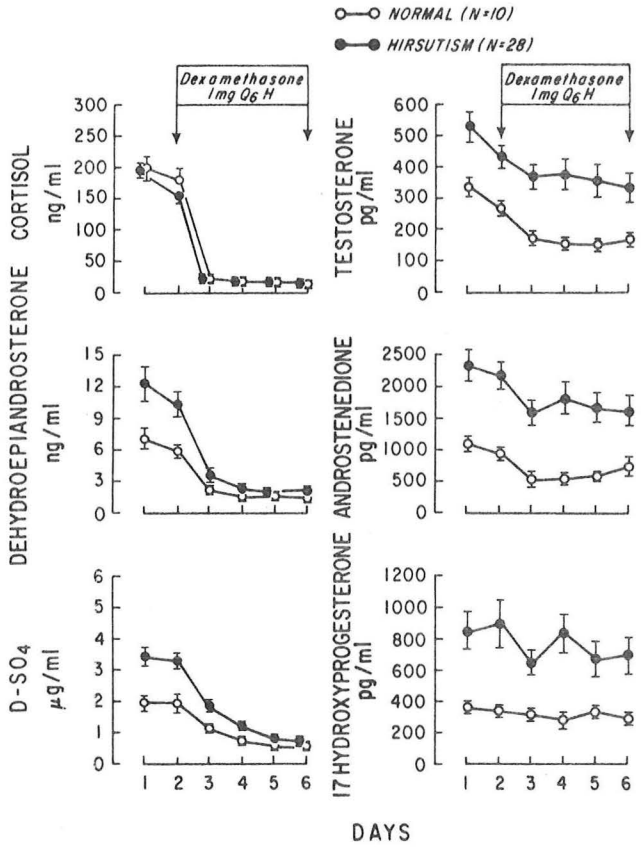

Figure 9

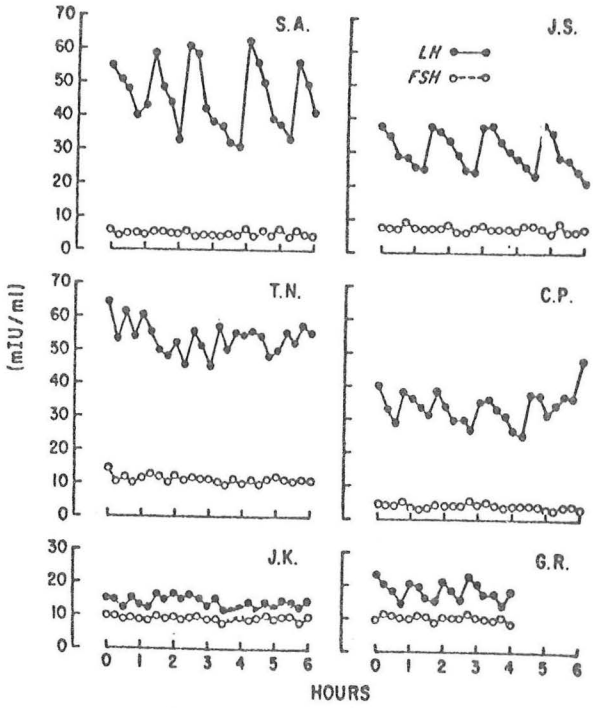

Figure 10

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D. Associated Disorders and Complications

Perhaps the most interesting association of PCOD is the simultaneous occurrence of acanthosis nigricans and insulin resistance (55-62). In some cases there are somatic abnormalities (56, 61) or lipodystrophy (60). The insulin resistance may be associated with clinical diabetes or only be apparent by noting an elevated plasma insulin level. The initial patients studied in detail had what has been termed the Type A defect associated with severe insulin resistance and an apparent primary abnormality of the receptor (57). Subsequently another young woman with PCOD, acanthosis nigricans, and insulin resistance was found to have a post-receptor defect (58, 59). In this patient the source of the excess androgen was shown to be the ovaries, and a decrease in androgen levels was associated with improvement in the acanthosis nigricans as had been noted in a previous patient (55). More recently the Type A insulin receptor disorder has been described in a family in which a male sibling had similar insulin resistance seemingly ruling out the PCOD as causative factor (61). The two patients in this family also had acral hypertrophy and muscle cramps. The male had acanthosis nigricans and apparently normal gonadal function. In spite of this apparent dissociation of the PCOD and insulin resistance in this family, the androgen excess of PCOD may result in more insulin resistance than that due to obesity alone in unselected patients with PCOD who do not have acanthosis nigricans (62). Burghen and coworkers found higher glucose and insulin levels in obese PCOD patients than obese controls with an average level of hyperinsulinemia following glucose nearly as high as some of the selected index patients (62). Thus insulin resistance (usually asymptomatic) may not be uncommon in PCOD.

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Recently there has been a great deal of interest in abnormal prolactin secretion in patients with PCOD (63-66). Hyperprolactinemia appears to be more common among patients with PCOD than normal women. PCOD patients with hyperprolactinemia may have galactorrhea and thus present like patients with the usual galactorrhea-amenorrhea syndrome. But, in contrast to the usual patients with hyperprolactinemia, these patients have elevated LH, testosterone, and estrone levels and normal estradiol levels instead of decreased LH and estrogen levels. The most likely explanation for the hyperprolactinemia is that consistently elevated estrone levels sensitize the pituitary lactotropes to overrespond to secretagogue agents. Whether this mechanism can eventually lead to the pituitary adenomas found in some patients with PCOD is not known (64).

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64. Futterweit W, Krieger DT: Pituitary tumors associated with hyperprolactinemia and polycystic ovarian disease. Fertil. Steril. 31:608-613, 1979.

65. Falaschi P, Del Pozo E, Rocco A, Toscano V, Petrangeli E, Pompei P, Frajese G: Prolactin release in polycystic ovary. Obstet. Gynecol. 55:579-582, 1980.

66. Alger M, Vazquez-Matute L, Mason M, Canales ES, Zarate A: Polycystic ovarian disease associated with hyperprolactinemia and defective metoclopramide response. Fertil. Steril. 34:70-71, 1980.

The increased extraglandular estrogen formation and the resulting hyperestrogenic state in PCOD is associated with an increased frequency of endometrial carcinoma (67-71). The endometrial cancer occurs at a younger age (less than 40) in PCOD patients than in other women with endometrial carcinoma and tends to be of a lower grade of malignancy and more superficial (70).

67. Jackson RL, Dockerty MB: The Stein-Leventhal syndrome: analysis of 43 cases with special reference to association with endometrial carcinoma. Am. J. Obstet. Gynecol. 73:161-173, 1957.

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V. PROPOSED MECHANISM OF THE PATHOPHYSIOLOGY

A. "Inappropriate Feedback"

In about 10% of PCOD patients, basal levels and pulsatile patterns of LH release are indistinguishable from those of a normal menstrual cycle. However, when these women are observed over an extended period of time the typical elevated LH levels are noted with only occasional occurrence of ovulatory events. Thus the chronic anovulatory state may not be fixed. The mechanism for this apparently functional derangement in the hypothalamic-pituitary-ovarian axis has been a source of much discussion. Is the "defect" in the hypothalamus, the pituitary, or the ovary? The answer appears to be "none of the above." The primary pathophysiological derangement is thought to be "inappropriate steroid feedback" (72, 73). The elevated LH levels are not caused by an inability of the hypothalamic-pituitary system to respond to the negative feedback effect of estrogen since the infusion of physiological amounts of estradiol results in a fall of plasma LH (Figure 11) and the antiestrogen clomiphene elicits a rise in plasma LH and FSH comparable to those observed in normal women (Figure 12) (72).

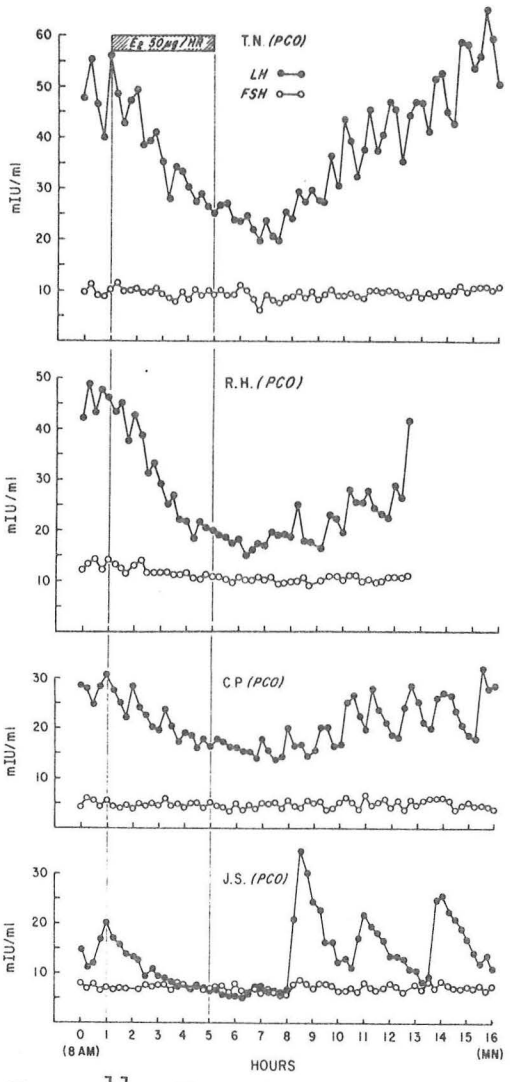

Figure 11. The variation of the increased amplitude and/or frequency of pulsatile secretion of LH with relatively constant low FSH release, and their prompt responses to the inhibitory effect of 17β-estradiol (E_2) infusion. (From Rebar et al.[42])

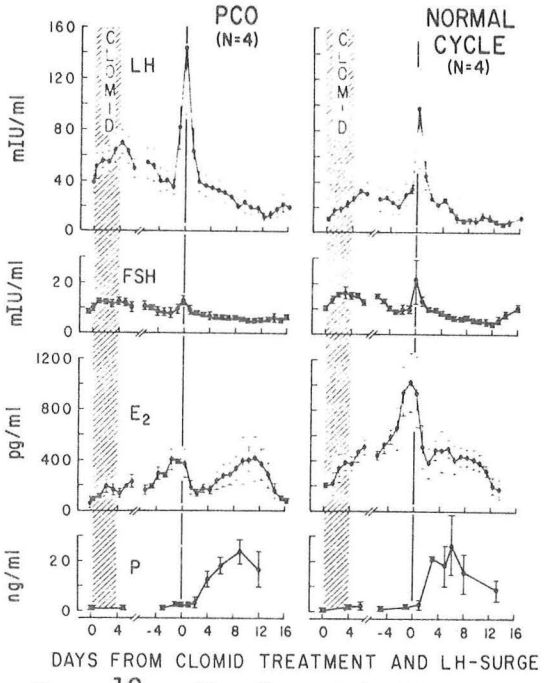

Figure 12. The effects of clomiphene citrate (Clomid 100 mg/day per 5 days) on the release of gonadotropins, and associated changes in ovarian steroids in PCO patients with chronic anovulation-amenorrhea, and in normal women during the early follicular phase of the cycle. P = progesterone. (From Rebar et al.[42])

The increased LH levels in PCOD are associated with an increased pituitary sensitivity to LHRH (72, 74). The chronically elevated and acyclical estrogen levels (primarily estrone) may be responsible for this increased LHRH sensitivity. In fact a good correlation can be demonstrated between estrogen levels and both the basal LH level (46) and the incremental LH response to LHRH (72). Chronically elevated estrogen levels can augment the pituitary sensitivity to LHRH by a direct action on the pituitary (6). Recently the finding of an increased sensitivity of LH levels in PCOD patients to a dopamine infusion has led to the hypothesis that these patients may be similar to normal women on the day of the midcycle surge, i.e., increased LH levels may be due to increased LHRH neuronal activity associated with a decreased inhibitory influence of dopamine (75).

The disparity between LH and FSH secretion in these patients may be explained by several factors: 1.) the negative feedback effect of estrogen is greater on FSH than on LH (6); 2.) FSH release is relatively insensitive to LHRH stimulation (72); and 3.) the multiple ovarian cysts could be a source of excessive amounts of inhibin which selectively inhibits the release of FSH (speculation). The proposed schema for the maintenance of the pathophysiology leading to chronic anovulation in PCOD is depicted in Figure 13. The cycle indicates how the increased

extraglandular estrogen formation, once established, can be self-perpetuating (32). In the absence of appropriate FSH release there is decreased follicle maturation. The excess ovarian androgen may also act locally to suppress follicle maturation (76).

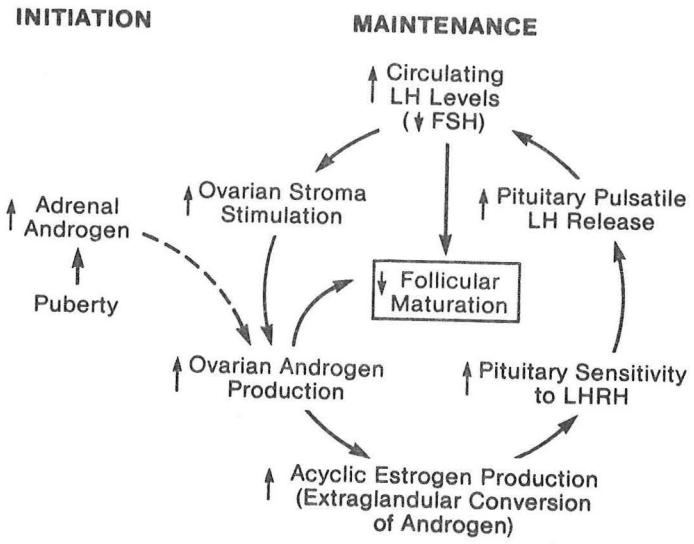

Figure 13

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73. Baird DT, Corker CS, Davidson DW, Hunter WM, Michie EA, Van Look PFA: Pituitary-ovarian relationships in polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 45:798-809, 1977.

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B. Structure-Function Relationships in Polycystic Ovaries

The cycle depicted in Figure 13 for the maintenance of anovulation in PCOD ovarian disease was derived from in vivo hormone dynamic testing and the known requirements for normal ovarian function. Recently detailed studies of structure-function relationships in polycystic ovaries in vitro have added support for the model (77-80). The numerous subcapsular follicular cysts in polycystic ovaries vary from 2 to 7 mm in diameter. They are usually lined with a thin layer of granulosa cells, but the most striking feature is the hyperplasia of the theca interna surrounding the cystic follicles. Isolated granulosa and theca tissue from normal and polycystic

ovaries have the same inherent steroidogenic capacity suggesting that differences are quantitative rather than qualitative (77, 80). The number of LH receptors is not increased in polycystic ovaries (79). Isolated PCOD theca tissue in culture produces several-fold more androgen than normal thecal tissue (80). Moreover, the surrounding stromal tissue may be an additional source of androgen (80). The androstenedione and testosterone not only enter the circulation but accumulate in follicular cysts in PCOD resulting in antral fluid levels of testosterone about 50-fold higher than normal (80). Prior in vitro studies of polycystic ovaries identified a decreased aromatase capacity (30). The follicular cysts in the ovaries of PCOD patients do not mature fully, and the absence of mature follicles results in low estrogen production (Figure 14) (78). To prove that these follicles only have a functional defect in aromatization, Erickson cultured 4-6 mm follicle granulosa cells with and without androstenedione as an aromatase substrate in the presence or absence of gonadotropins. FSH (but not LH) in the presence of substrate stimulated estrogen production to a level similar to granulosa cells from normal 6 mm follicles (Figure 15) (78). Thus the low aromatase activity in PCOD is secondary to the decreased FSH concentration rather than an intrinsic ovarian abnormality. The combination of increased LH and low FSH would be anticipated to result in excess androstenedione formation with little estrogen formation.

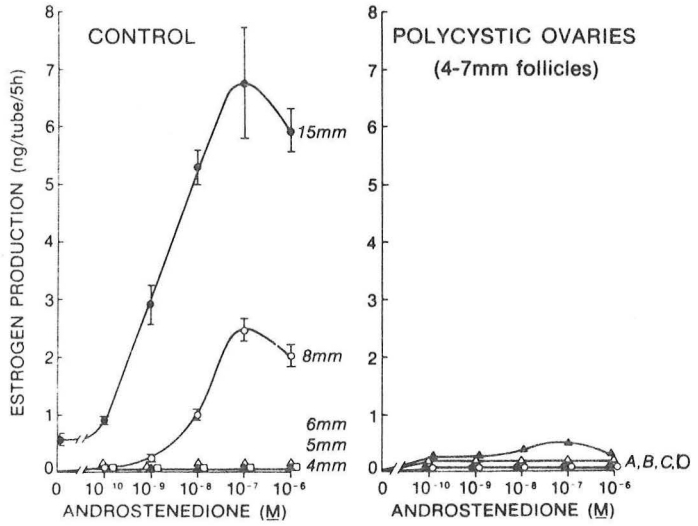

Figure 14

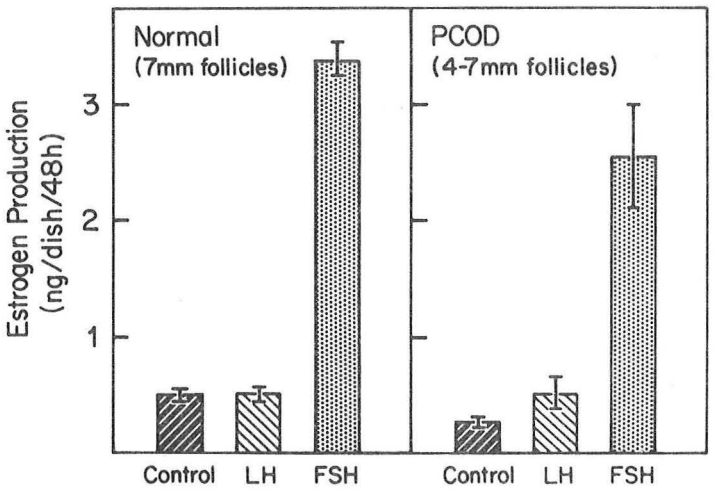

Figure 15

77. Wilson EA, Erickson GF, Zarutski P, Finn AE, Tulchinsky D, Ryan KJ: Endocrine studies of normal and polycystic ovarian tissues in vitro. Am. J. Obstet. Gynecol. 134:56-63, 1979.

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C. Cause of the Adrenal Androgen Excess in PCOD

The discussion of the "cycle" leading to persistent anovulation in PCOD suggests how ovarian androgen excess can be maintained, but it does not account for the confirmed adrenal hypersecretion of DHEA and other potential testosterone precursors. Early studies concluded a partial adrenal hydroxylase deficiency must be present to account for the excretion of certain metabolites of adrenal steroids (81, 82). More recently Givens et al observed adrenal hypersecretion of androstenedione in response to ACTH in some hirsute patients with concurrent ovarian hypersecretion of androgens (47). However, most of Givens's patients had idiopathic hirsutism (see below).

Lachelin et al have recently reevaluated the role of the adrenal in PCOD by using multiple sampling throughout a 24-hour period to compare circadian variation in relationship to cortisol levels as evidence of response to endogenous ACTH (28) and to determine mean plasma hormone concentrations (83). Patients with PCOD had a blunting of the midnight nadir for androstenedione, testosterone, and 17-hydroxyprogesterone; but the patterns of cortisol, DHEA, androstenediol, pregnenolone, and 17-hydroxypregnenolone were qualitatively and quantitatively similar to the circadian variation seen in normal women. The blunting of androstenedione, testosterone, and 17-hydroxyprogesterone nadirs probably represent the ovarian contribution (recall the incomplete dexamethasone suppression in Figure 9). Adrenal sensitivity (assessed by the response to a pulse of ACTH) was normal, but adrenal capacity (assessed by the response to ACTH infusion) was increased in PCOD in so far as the incremental changes in DHEA, progesterone, 17-hydroxyprogesterone, and 17-hydroxypregnenolone were greater than those in normal women. Cortisol responses were not different for the two groups of subjects. The fact that the differences between normal subjects and PCOD patients were detected only in response to sustained ACTH stimulation, which does not occur under physiological conditions, indicates the absence of overt enzymatic abnormalities in PCOD. The abnormality demonstrated is probably most compatible with a secondary effect of the ovarian androgen excess on adrenal steroidogenesis which has so far only been demonstrated in vitro with animal tissues (84, 85).

81. Cox RI, Shearman RP: Abnormal excretion of pregnanetriolone and Δ^5-pregnenetriol in the Stein-Leventhal syndrome. J. Clin. Endocrinol. Metab. 21:586-590, 1961.

82. Leventhal ML, Scommegna A: Multiglandular aspects of the Stein-Leventhal syndrome. Am. J. Obstet. Gynecol. 87:445-454, 1963.

83. Lachelin GCL, Barnett M, Hopper BR, Brink G, Yen SSC: Adrenal function in normal women and women with the polycystic ovary syndrome. J. Clin. Endocrinol. Metab. 49:892-898, 1979.

84. Sharma DC, Forchielli E, Dorfman RI: Inhibition of enzymatic steroid 11β-hydroxylation by androgens. J. Biol. Chem. 238:572-575, 1963.

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D. Speculation on the Pathogenesis

While both adrenal and ovarian androgens may be a substrate for extraglandular estrogen formation to maintain abnormal endocrine profile characteristic of PCOD, these processes do not account for the initiation of the disorder. The etiology of PCOD is unknown. Yen has proposed that this syndrome originates as an adrenal disorder during the early phase of sexual maturation (86). Most patients (or their parents) date the onset of excessive hair growth, obesity, and anovulation to the peripubertal phase of development. The theory of the adrenarche, a progressive increase in adrenal androgen secretion coincident with sexual maturation, is now well established (87, 88). Adrenarche is not associated with increased levels of gonadotropins, nor is it caused by ACTH-mediated adrenal androgen secretion, since a parallel increase in cortisol secretion does not occur. Elevated androgen levels associated with an exaggerated "adrenarche" could result in the initial substrate for the extraglandular estrogen formation which in turn would induce an elevated LH/FSH ratio and the associated ovarian androgen secretion (Figure 13) (86).

The possibility that adrenal androgen excess might lead to secondary development of PCOD is supported by the coexistence of PCOD in young patients with congenital adrenal hyperplasia (89, 90) and a patient with a virilizing adrenal adenoma (91). However, these disorders are not present in the overwhelming majority of patients. Perhaps an adrenal stimulating factor other than ACTH will be identified and shown to be increased in PCOD patients. Such a factor has been postulated to account for the increase in zona reticularis size at the time of adrenarche in association with increased DHEA-S secretion (92). Until such a factor is found we will have to settle for an "exaggerated adrenarche" as the tentative explanation.

The relationship of obesity to the syndrome is not clear. On the one hand there is some evidence that estrogen may stimulate adipocyte precursor replication (93), and thus increased estrogen formation early in adrenarche could presumably lead to the obesity. Alternatively obese women are known to have a higher rate of extraglandular estrogen formation (44). Studies in massively obese women revealed an increased androstenedione level with decreased TeBG binding capacity, but gonadotropins and testosterone levels were similar to lean controls (94). In a recent abstract comparing obese adolescent girls with and without oligomenorrhea to normal weight controls, only the group with oligomenorrhea had elevated LH, androstenedione, DHEA, testosterone, and estrone levels (95). Thus obesity may be present in almost half of the patients with PCOD, but it is not sufficient in itself to result in the typical endocrine pathophysiology.

86. Yen SSC, Chaney C, Judd HL: Functional aberrations of the hypothalamic-pituitary system in polycystic ovary syndrome: a consideration of the pathogenesis. In The Endocrine Function of the Human Ovary, VHT James, M Serio, G Giusti (eds), Academic Press, New York, 1976, pp 373-385.

87. Hopper BR, Yen SSC: Circulating concentrations of dehydroepiandrosterone and dehydroepiandrosterone sulfate during puberty. J. Clin. Endocrinol. Metab. 40:458-461, 1975.

88. Ducharme J-R, Forest MG, De Peretti E, Sempe M, Collu R, Bertrand J: Plasma adrenal and gonadal sex steroids in human pubertal development. J. Clin. Endocrinol. Metab. 42:468-476, 1976.

89. Bergman P, Sjogren B, Hakansson B: Hypertensive form of congenital adrenocortical hyperplasia. Analysis of a case with co-existing polycystic ovaries. Acta Endocrinol. 40:555-564, 1962.

90. Lucis OJ, Hobkirk R, Hollenberg CH, MacDonald SA, Blahey P: Polycystic ovaries associated with congenital adrenal hyperplasia. Can. Med. Assoc. J. 94:1-7, 1966.

91. Kase N, Kowal J, Perloff W, Soffer LJ: In vitro production of androgens by a virilizing adrenal adenoma and associated polycystic ovaries. Acta Endocrinol. 44:15-19, 1963.

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93. Roncari DAK, Van RLR: Promotion of human adipocyte precursor replication by 17β-estradiol in culture. J. Clin. Invest. 62:503-508, 1978.

94. Kopelman PG, Pilkington TRE, White N, Jeffcoate SL: Abnormal sex steroid secretion and binding in massively obese women. Clin. Endocrinol. 12:363-369, 1980.

95. Kaufman ED, Mosman J, Yen SSC: Characterization of gonadotropin release patterns and basal estrogen and androgen levels in the obese adolescent female. Clin. Res. 29:109A, 1981.

VI. DIFFERENTIAL DIAGNOSIS

The diagnoses of PCOD can usually be made from the history, the characteristic clinical features and the demonstration of chronic anovulation. Although most gynecologists are comfortable in inferring anovulation in patients with oligo- or amenorrhea based on the presence of abundant clear thin cervical mucus as evidence of estrogen action, internists are likely to be more comfortable with the Provera challenge test. If physical examination is not indicative of pregnancy and urine hCG is negative, evidence of the presence of estrogen action is sought by the oral administration of a progestin such as medroxyprogesterone acetate (Provera) 10 mg p.o. daily for 5 days. If a proliferative endometrium is present (indicative of endogenous estrogen production) it will be converted to the secretory stage by the Provera; within a week of stopping the progestin, withdrawal bleeding should occur (Figure 16). If withdrawal bleeding does ensue, the patient must have one of several disorders that result in chronic anovulation (of which PCOD is the most common in women who come to medical attention). The absence of uterine bleeding following progestin withdrawal indicates either estrogen deficiency or a hormonally unresponsive endometrium (Figure 16). (Measurement of plasma prolactin concentration at the start of the Provera helps define another common cause of amenorrhea.)

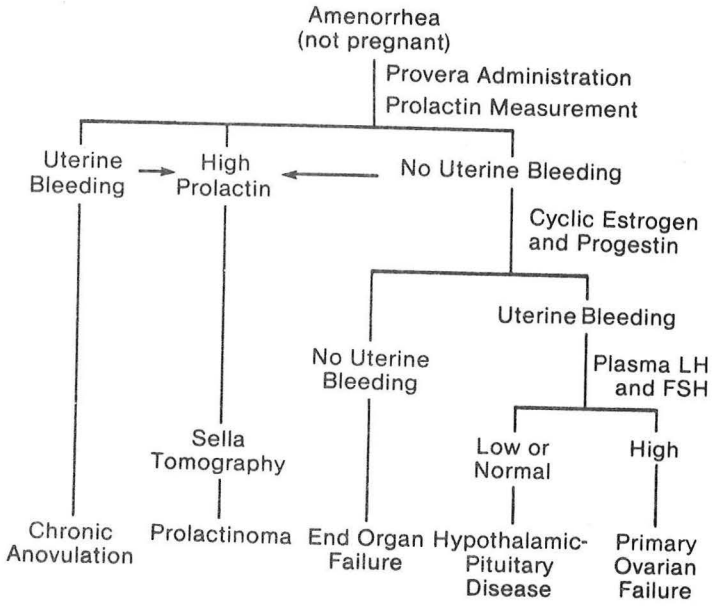

Figure 16

Measurement of plasma LH and FSH concentrations may be useful in supporting the diagnosis with the finding of an increased LH and low FSH. If hirsutism is present, a plasma testosterone concentration should be determined. Although a normal value for the total testosterone concentration may be present in women with increased testosterone production (see above), the finding of a very high value may be useful. A testosterone level greater than 2.0 ng/ml or rapid progression of severe virilization should suggest the possibility of a virilizing tumor rather than PCOD. (As demonstrated by the description of Patient 2, some women with virilization and this degree of testosterone elevation may still have a functional ovarian disorder.)

The differential diagnosis of the chronic anovulation of PCOD includes the increased extraglandular estrogen formation present in hyperthyroidism, liver disease, and obesity (44), administration of estrogens, and estrogen-producing tumors. The differential diagnosis of the androgen excess of PCOD includes the functional and neoplastic ovarian and adrenal disorders of androgen overproduction in women (Table IV), conditions which usually lead to inappropriate feedback and anovulation.

Table IV. Disorders of Androgen Overproduction in Women

Ovarian disorders		
	Functional --	Polycystic ovarian disease
		Idiopathic hirsutism
		Luteoma of pregnancy
	Neoplastic --	Endocrine active tumors
		Tumor stimulation of stroma
Adrenal disorders		
	Functional --	Congenital adrenal hyperplasia
		Cushing's disease
	Neoplastic --	Adrenal adenoma
		Adrenal carcinoma

A. Idiopathic Hirsutism

Idiopathic hirsutism is a diagnosis of exclusion. It should not be made if any of the other signs or symptoms of PCOD are present (22, 34). Specifically the history of normal predictable menses should be sought as confirmation of normal ovulation. It is not sufficient to state that the patients have normal-sized ovaries on pelvic exam since this is clearly compatible with PCOD. Also there should be no history of ingestion of drugs recognized to cause hirsutism (phenytoin, diazoxide, minoxidil). In those studies of androgen production or free testosterone levels in hirsute women in which the individual data are reported or in which data are analyzed separating "eumenorrheic" women from those with oligomenorrhea (54, 96), there appears to be some overproduction of androgen by the ovary with lesser elevations of testosterone and androstenedione than seen in PCOD. Patients with idiopathic hirsutism either a) represent the extreme end of a normal distribution of androgen production rate, b) have a subtle endocrine disorder as yet not understood, or c) have PCOD in evolution.

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B. Virilizing Ovarian Tumors

These neoplasms are usually unilateral. They vary in size from 1 to more than 30 cm in diameter, but a palpable mass is detected only about two-thirds of the time (97). Tumors which are endocrinologically active and secrete androgens directly include gonadal stromal tumors (arrhenoblastomas), Sertoli-Leydig cell tumors, hilus cell tumors, adrenal rest tumors, and granulosa-theca cell tumors. All overproduce androgens, usually testosterone with eventual defeminization and severe virilization. However, hirsutism may be the first manifestation of the virilizing process. The rapidity of progression of symptoms and a plasma testosterone level above 2.0 ng/ml should suggest this possibility as indicated above. Since a third of tumors are not palpable on bimanual examination, preoperative venous catheterization may be helpful in documenting the source of the excess androgen (98).

Brenner, cystic teratoma, mucinous cystadenomas, and Krukenberg tumors lead to androgen excess by stimulating the surrounding ovarian stroma to hypersecrete androgen (99, 100). Tumors that have this capacity may be benign or malignant, primary or metastatic. The mechanism for stimulation of the stroma is unknown. The endocrine profile is similar to the secretory tumors. There appears to be an increased occurrence of ovarian tumors in patients with PCOD (101, 102). It is conceivable that in some instances the PCOD is secondary to the tumor hypersecretion of androgen as in the adrenal androgen excess discussed regarding the pathogenesis of PCOD.

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C. Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) in females is usually suspected because of some degree of virilization detectable at birth. The most common enzymatic block leading to the disorder is 21-hydroxylase deficiency (about 95% of all CAH). Deficiency of 11β-hydroxylase can also lead to a similar degree of virilization during embryogenesis, but has the additional feature of hypertension. The clinical history and the marked elevation of plasma 17-hydroxyprogesterone and its urinary metabolite pregnanetriol usually present no problem in the differential diagnosis in the typical patients. However, it is now clear that some patients with CAH may first come to medical attention after pubescence. Patients with 21-hydroxylase deficiency (103, 104) and patients with 11-hydroxylase deficiency (105, 106) have been described with hirsutism and oligomenorrhea as the only manifestations of CAH (i.e., there was no clitoromegaly). Interestingly, in two patients the plasma LH was elevated and a diagnosis of PCOD had been previously made to account for the mild elevation in testosterone and the anovulation (103). Family studies in these patients confirmed them to be mildly affected homozygotes. Fortunately in these patients, as well as in the others described with adult onset 21-hydroxylase deficiency (104), the baseline plasma 17-hydroxyprogesterone was greater than 3.0 ng/ml (the upper limit for normal women in the follicular phase of the menstrual cycle). Presumably the LH is elevated in these women because of increased extraglandular estrogen formation.

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D. The Cushing Syndrome

Oligo- or amenorrhea and hirsutism are common in women with Cushing syndrome. The causes of the chronic anovulation and the irregular or absent menses include a central neurotransmitter mechanism (especially in Cushing's disease) (107) as well as abnormal feedback from extraglandular estrogen formation from the excess adrenal-derived testosterone present in all patients with Cushing syndrome (108). In time, an overproduction of ovarian androgen may result from the chronic anovulation and PCOD-like ovaries may result (32). In women with truncal obesity, plethora, and hypertension an overnight dexamethasone suppression test should be performed to rule out this diagnosis.

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E. Virilizing Adrenal Tumors

Most adrenal adenomas and carcinomas produce excess DHEA and androstenedione leading to marked elevations in urinary 17-ketosteroids (109). Plasma DHEA-S has been used as a marker for such abnormal adrenal androgen secretion (110). Initially it was thought that testosterone elevations in such patients were the result of peripheral conversion of secreted androstenedione. There are now at least five reports of women with testosterone-secreting adrenal tumors (111-115). In most instances the urinary 17-ketosteroids are not elevated in the setting of plasma testosterone concentrations in the normal male range (3.0 to 10.0 ng/ml). In addition, a source of greater confusion is the evidence of gonadotropin responsiveness of the testosterone secretion in some instances (111-113). All of these patients have had frank virilization. Virilizing ovarian tumors are much more common than these tumors. However, it is thus important to consider preoperative selective catheterization for localization of the source of the testosterone excess in women without a palpable ovarian mass who are suspected of having an ovarian tumor.

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VII. THERAPY

The therapy of PCOD has two distinct aims: reversal of chronic anovulation and treatment of hirsutism. The anovulation may not be of concern to some women who do not desire fertility, and periodic spontaneous menses may provide sufficient prophylaxis to endometrial hyperplasia. If hirsutism is minimal in these patients as well, no therapy of PCOD is required. The treatments designed for reversal of the anovulation may also reduce the hirsutism.

A. Reversal of Anovulation

The effectiveness of clomiphene citrate, an antiestrogen, for inducing ovulation in patients with PCOD is well established (116, 117). It increases FSH (and LH) secretion by blocking the feedback inhibition of endogenous estrogen. The drug is given orally in a dose of 50 mg per day for five days starting on the fifth day of the menstrual cycle which is usually induced with Provera in patients with chronic anovulation. Follicle maturation occurs with an increase in the plasma estradiol level followed by the positive feedback effect on the hypothalamic-pituitary unit and the resultant ovulatory surge of LH and FSH (Figure 12). If ovulation occurs it is usually between 5 and 10 days after completing the course of clomiphene. Over 90% of treated patients ovulate on this regimen, and 50% of patients become pregnant. If a dose of 50 mg is ineffective, 100 or 150 mg per day may be tried. The regimen needs to be individualized for optimal results (117). The incidence of multiple gestations is increased to 10%. Although abdominal discomfort, nausea, vomiting, headaches, and vasomotor symptoms occur in some patients, the ovaries rarely enlarge. This is the preferred method of ovulation induction in PCOD. Ovulation may be confirmed by shift in basal body temperature or the finding of a plasma progesterone concentration of 5 mg/ml or greater 14 to 16 days after completing treatment. Testosterone and androstenedione levels decrease in association with return of ovulation (72).

More difficult and expensive is induction of ovulation with human menopausal gonadotropins. Although it may be effective in women with PCOD who do not respond to clomiphene (118), it is associated with some serious side effects due to hyperstimulation of the ovaries and requires monitoring of plasma estradiol or urinary estrogens. Human menopausal gonadotropins contains both LH and FSH in equal quantities. Since LH levels are already elevated in PCOD, it would seem desirable to only give FSH. There are now two reports of successful induction of ovulation using purified human pituitary FSH (78, 119) (Figure 17).

Wedge resection of part of each ovary has been used to restore cyclic menses. The average success in restoring cyclic menses in about 80%, and over 60% of patients are subsequently able to become pregnant (30). In most, but not all, patients the successful results of wedge resection are permanent. Recent studies have demonstrated a marked but transient reduction of androstenedione levels and a more persistent decrease in testosterone levels (Figure 18) (120-122). Interestingly, in the one patient in whom DHEA levels were measured (121), wedge resection resulted in a fall in plasma levels. This would support the concept that the changes

in adrenal androgen secretion are secondary phenomena. The mechanism for reversal of anovulation by wedge resection is thought to be removal of a significant mass of androgen-secreting stromal tissue, thus temporarily decreasing the plasma androgen levels and the available substrate for extraglandular estrogen formation (and breaking the cycle shown in Figure 13).

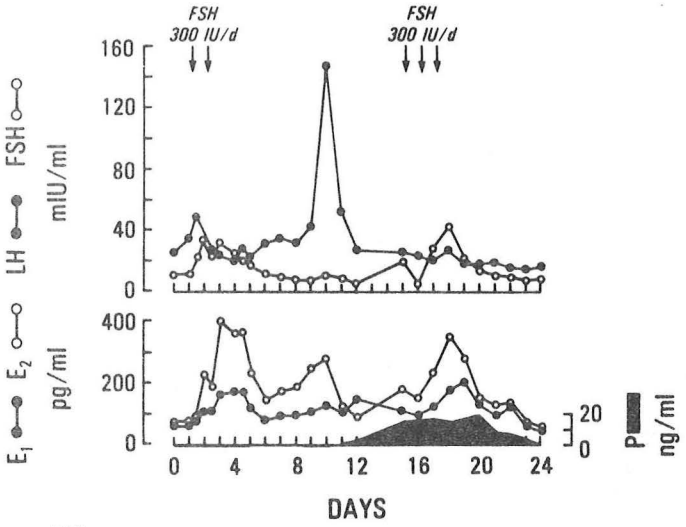

FIG. 17 Effect of purified FSH on serum gonadotropin and E levels in one patient with PCO. The first administration was apparently followed by ovulation, as documented by an LH surge, elevated P levels, and subsequent menses. Administration of FSH in the luteal phase resulted in increased circulating E levels but did not produce any apparent effect on luteal function.

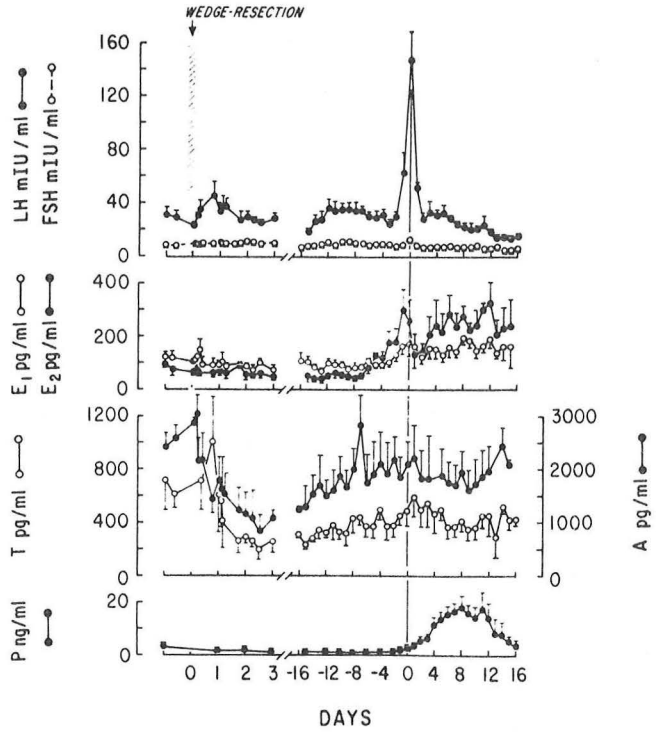

Figure 18

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B. Treatment of Hirsutism

Approaches to the treatment of hrisutism in women with PCOD have included attempts to lower plasma testosterone and/or to block testosterone action at the receptor level. Oral contraceptives of the estrogen-progestin combination type are effective in lowering the plasma androstenedione and testosterone concentration by 50% at three weeks into the course of therapy (123). The suppression of testosterone is correlated with the decrease in LH. Oral contraceptives also induce an increase in TeBG binding capacity, decreasing the clearance rate of testosterone and return free testosterone concentrations toward normal (124, 125). Glucocorticoids are also reported to be effective in treating the hirsutism of PCOD and may even reverse the chronic anovulation (31). Since most patients with PCOD have some adrenal androgen excess it is not surprising that reducing this component might partially decrease the total androgen levels and the substrate for extraglandular estrogen formation. In addition, glucocorticoids appear to decrease ovarian androgen production (14, 54). The regimen used by some clinicians is dexamethasone 0.5 mg p.o. at bedtime. The safety of long-term treatment with this regimen is not known. There is certainly a risk of suppression of the pituitary-adrenal axis.

Spironolactone is an aldosterone antagonist which also is a weak competitor for androgen binding to the androgen receptor. In moderate doses it also blocks testosterone synthesis. The administration of 25 mg twice daily of spironolactone to hirsute women is associated with a 50% reduction in testosterone production rate at 6 months of therapy (126). Plasma testosterone levels also decreased by 50%. In this study and another one using a different regimen only administering the drug 18 days of the cycle (127) a subjective and a semiobjective means of grading hirsutism suggested a decreased rate of hair growth first evident 3 months after beginning therapy. Cyproterone acetate is an antiandrogen which competes at the receptor level and is not available in this country. It has been used in other countries in combination with estrogen to treat hirsutism (128, 129). Recently cimetidine, a drug first suspected of being an antiandrogen because of the development of gynecomastia in men treated with it for peptic ulcers, has been used to treat hirsutism. In a small study in which 5 women were given cimetidine 300 mg orally five times daily for three months unblinded semiquantitative assessment of rate of hair growth seemed to indicate a beneficial effect (130).

Women with PCOD and hirsutism who do not wish reversal of anovulation by the means described above may be given oral contraceptives. However, if the hirsutism is mild, it might not seem justified to expose the patients to the risk of the oral contraceptives. The experience with spironolactone or cimetidine is not extensive enough to recommend their routine use, but for selected patients it would seem reasonable to try spironolactone. Decrease in androgen production or action may not be followed by a satisfactory decrease in the rate of hair growth. Local measures such as electrolysis may be necessary in such instances.

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