

REFERENCES

- Abraham , G. E. ; and Chakmakjian , Z.H. (1974) :
Plasma steroids in hirsutism. J.
Obstet. Gynaecol., 44 , 171.
- Abraham , G. E. ; Maroulis , G. B. ; Buster , J. E. ;
Chang , R. J. ; and Marshall , J. R.
(1975) : Effect of dexamethasone on
on serum cortisol and androgen levels
in hirsute patients. Obstet.
Gynaecol., 47 , 395.
- Abraham , G. E. ; Maroulis , G. B. ; Buster , J. E. ; et al.
(1976): Effect of dexamethasone on
serum cortisol and androgen levels in
hirsute patients. Obstet. Gynaecol. ,
47 , 395.
- Abraham , G. E. ; and Buster , J. E. (1976) :
Peripheral and ovarian steroids in
Ovarian hyperthecosis. Obstet. Gynaecol.
47 , 581.

Abraham , G. E. ; Maroulis , G. B. ; Boyers , S. P. ; et al.

(1981) : Dexamethasone suppression test
in the management of hyper androgenized
patients. Obstet. Gynaecol., 57 , 158

Angeli , A. ; Boccuzzi , G. ; Bisbocci , D. ; Fonzo , D. ;

Frajria R.; de Sanchs ,C. ;
and Ceresa , F. (1976) :

Effect of cyproterone acetate therapy
on gonadotropin response to synthetic
luteinizing hormone - releasing hormone
(LRH) in girls with idiopathic
precocious puberty. J. Clin. Endocrinol.
Metab., 42 , 551.

Bardin , C. W. ; Lipsett, M. B. ; Edgcomb, J. H. ; and
Marshall, J. R. (1967) :

Studies of testosterone metabolism
in a patient with masculinization due
to stromal hyperthecosis. N. Engl. J.
Med. , 277 , 399.

Bardin , C. W. ; and Lipsett , M. B. (1967) :

Testosterone and androstenedione blood
production rates in normal women and
women with idiopathic hirsutism or
polycystic ovaries. J. Clin. Invest.,
46 , 891.

Prolactin response to thyrotropin - releasing hormone was normal in the hirsute women. No significant relationship between prolactin and steroid hormones values. On the other hand, mean dehydro epiandrosterone and its sulfate, and androstenedione were higher in the group of ten hirsute women with slightly elevated prolactin concentrations than in the group with normal concentrations, but the difference was not significant. Thus serum prolactin is often slightly elevated in hirsute women with ovarian hyperandrogenism (Buvat et al, 1982).

Urinary Steroids in hirsutism :

The amounts of androstenediol (the main metabolite of dihydro testosterone) and testosterone glucuronide excreted in the urine of 17 normal men, ten normal women and ten women with idiopathic hirsutism were measured by Mauvais - Jarvis et al, in 1973. In women with idiopathic hirsutism. The mean urinary excretion of testosterone was in the normal range for women, whereas

the mean excretion of androstenediol was elevated to levels found in normal men. This elevation is compatible with an extensive transformation in extra hepatic tissues of testosterone or other androgen precursors to androstenediol. Most hirsute patients have elevated androgens levels upon thorough evaluation. If only urinary 17 - Ketosteroids are measured, only 15% of hirsute women will have elevated values (Maroulis et al, 1977), and it is not always clear what these values signify (Judd et al , 1977).

Adrenal and Ovarian vein catheterization

To determine the origin of the excessive testosterone, percutaneous bilateral adrenal and ovarian vein catheterization were performed and effluent blood samples obtained for androgen measurement. Kirschner and Jacobs, (1971) found that in 9 of the 13 women studied, the major source of androgen was ovarian. In the remaining four women, androgen originated from both the ovaries and adrenal glands. Following dexamethasone administration there was a decrease in plasma testosterone and androstenedione in the four women whose androgen originated from both adrenals and ovaries and also in three out of the nine women whom androgen originated from the ovaries.

Rosenfield et al, (1972) using dexamethasone suppression criteria, concluded that 85% of oligomenorrheic hirsute women had excessive ovarian production of androgens, and Kirschner et al, (1976) using catheterization criteria, concluded that 90% of a group of predominately oligomenorrheic hirsute

women had excessive ovarian androgen production.

Givens et al, (1974) found that an elevation of serum testosterone levels without an elevation of urinary 17 - Ketosteroid levels points to the presence of an ovarian lesion because the adrenal does not convert precursors to testosterone. However, exceptional adrenal tumours possess pathways of testosterone biosynthesis without directly oversecreting enough androstenedione or dehydroepiandrosterone to cause an elevation of urinary 17 - Ketosteroid levels.

Abraham et al, (1976) , Maroulis et al, (1981) found that the evaluation of hirsutism must include the measurement of plasma levels of androgen. Among the adrenal androgens , dehydroepiandrosterone sulfate is a good choice to study because it attains the highest levels in normal individuals, its levels remain relatively constant despite the diurnal variation of other adrenal androgens, it suggests specifically adrenal rather than ovarian disease, and its levels have been

found to be elevated in patients with adrenal androgen excess of various causes.

Treatment of Hirsutism

Treatment of hirsutism depends of course upon the cause of the excess androgen secretion in the individual case. There are various methods of suppressing the excess androgen production after locating its source. They can be summarized in the following :

Dexamethasone :

Dexamethasone can be used to suppress the excess androgen production of adrenal origin, but as the source of androgen excess in hirsute women is usually the ovaries, it is rarely used alone but usually in combination of other drugs which suppress the ovarian androgen. Dexamethasone is usually preferred than other steroids because it is a potent steroid and has least of side effects.

Nightly dexamethasone administration resulted in prompt and sustained suppression of cortisol , dehydroepiandrosterone and androstenediol. The

nocturnal rises of these hormones were also completely suppressed. The amount of suppression was equal to or greater than that reported earlier with short term, high dose dexamethasone administration in both hirsute and normal women using only morning samples (Bardin et al, 1968 ; Abraham et al, 1976 ; and Judd et al, 1977). Also nightly dexamethasone administration was associated with reduction of serum androstenedione and testosterone and obliteration of their diurnal fluctuations. The magnitude of these reductions was less than were reported by earlier investigators using short term, large dose dexamethasone administration using only morning samples (Turbridge et al, 1973 ; Abraham et al; 1975 ; and Judd et al, 1977).

Rosenfield et al, (1980) found that a single 0.5 mg dose of dexamethasone at bed time is the usual starting dose and it is adjusted depending upon the androgen level. This generally lessens adrenal secretion for most of the day. Therapy at this level usually doesnot impair recovery of adrenal reserve. However, cortisol levels

should be measured while the patient is receiving dexamethasone and if the morning cortisol level is less than .003mg/ 100ml, the patient would be at risk of developing cushingoid changes and should be advised to increase medication in times of stress. Dexamethasone doses over 0.75 mg/ day are likely to result in cushingoid changes over along period of time

Lachelin et al, (1982) found that nightly dexamethasone administration for one month resulted in marked suppression of dehydro epiandrosterone , testosterone, androstenediol and cortisol. For testosterone the mean percent decreases of the twenty four hours transverse means were 15% and 46% for the polycystic ovarian disease and normal subjects, respectively. For androstenedione the mean percent decreases were only 7% and 20%, respectively. The diurnal variation of all steroids disappeared with dexamethasone.

HoYuen and Mincey, in 1983 found that the administration of glucocorticoids to hyperandr-

ogenic hirsute women resulted in a significant suppression of androstenedione plasma levels and 17 - Ketosteroid excretion. Although statistically insignificant, testosterone and luteinizing hormone concentrations declined to a mean of 65% and 51% of pretreatment values, respectively. Clinically, beneficial effects were observed on the hirsutism & menstrual dysfunction in these women.

Oral Contraceptive :

Since oral contraceptives have been used by many workers to suppress excess androgen secretion by the ovary and in locating the source of androgen excess in hirsute patient, use was made of this to treat these patients. Since the ovaries have been found to be the main source of androgen excess rather than the adrenal, oral contraceptives pill seem to be a useful drug in treatment of such condition. The choice of the suppressing agent may be critical.

Estrogen alone is a poor suppressant of

lutenizing hormone in hirsute women (Kirschner et al, (1970)). Plasma testosterone is increased and not decreased in hirsute women given norethindrolone 1 mg- mestranol 0.08 mg (Easterling et al, 1974).

Further investigation is needed to evaluate the relative effectiveness of various progestin-estrogen combinations in suppressing androgenic hormones in hirsutism.

The effectiveness of two oral contraceptives in suppressing plasma androstenedione (A) , testosterone (T) , luteinizing hormone (LH) and follicle stimulating hormone (FSH) and in stimulating testosterone - estradiol - binding globulin (TEBG) was evaluated in 39 hirsute women , by Givens et al, in 1976. Twenty seven hirsute women received norethindrolone 2 mg, mestranol 0.1 mg (Group I) and 12 received norgestrol 0.5 mg - ethinyl estradiol 0.05 mg (Group II).

Hormone assays were performed before treatment and at the end of 3 weeks of therapy.

subjectively reported a decrease in the rate of hair growth and / or a decrease in the amount of facial hair.

Gordon et al, (1970) showed that medroxyprogesterone reduced the plasma levels of testosterone in both normal men and women.

Correa de Oliveira et al, in 1975 treated 24 hirsute female patients with 100 mg of depo-medroxy progesterone acetate intramuscularly by every 15 days. Twenty - three showed definite improvement from their abnormal hair growth. All patients with initially elevated 17 - Ketosteroids in 24 - hours urine collected, showed a decrease of these metabolites with treatment. In eleven patients the initial plasma testosterone level was elevated and returned to normal values with treatment. The first patient who was submitted to this therapy stopped the treatment for five months and started having abnormal hair growth again. With other patients after initial treatment with depo-medroxy progesterone acetate i.m , they started using contraceptive

pills containing medroxy progesterone, this maintained the reduced ectopic hair growth. The most important side effect was amenorrhea .

Cyproterone acetate :

Cyproterone acetate is an antiandrogen, the chemical structure of which is similar to that of chlormadinone. The acetylated compound has strong progestogenic activity in addition to its anti - androgenic activity (Vokaer and Kridelka (1963).

The anti androgen properties arise from the drug's competition with testosterone at endorgan receptors (Viogt et al, 1968 ; Neumann, 1971).

It is contraindicated in liver disease. It influences the enzymatic activity of the liver, especially the glucuronyl transferase (Elert , 1969) , although, Burchardt and Agrapidakis , (1972) found no liver damage after three and half years treatment.

There is a number of studies of its effect in hirsute women. Hammerstein and cupceancu, (1969) recommended a sequential regime of cyproterone acetate (C A) with 100 to 200 mg daily from the 5th to the 14th days of menstrual cycle and .05mg of ethinyl - estradiol from the 5th to 25 th days of the cycle. Ethinyl - estradiol was used to inhibit ovulation to obviate the possibility of pregnancy during treatment because intrauterine feminization of male fetuses after administration of cyproterone acetate to pregnant rats has been reported (Hamada et al, 1963).

Ismail et al, in 1974 using the above regime, reported a marked reduction in hirsutism after 12 months of therapy. There was a significant increase in the rate of hair growth following cessation of cypro terone acetate alone, but not ethinyl - estradiol. Both plasma and urinary testosterone levels were reduced during therapy

Different figures of success reported , using cyproterone acetate in treatment of

Bardin , C. W. ; Hembree , W. C. ; and Lipsett , M. B.

(1968) : Suppression of testosterone and androstenedione production rates with dexamethasone in women with idiopathic hirsutism and polycystic ovaries. J. Clin. Endocrinol. Metab., 28 , 1300.

Bardin , C. W. ; and Kirschner , M. A. (1971) :

In Sunderman F.W. and F.W. Sunderman (eds.), The laboratory diagnosis of endocrine diseases. Warren H. Green , Inc. St. Louis.

Barnes , A. B. (1979) : Menstrual history of young women exposed in utero to diethyl stilbesterol. Fertil. Steril., 32 , 148.

Baxendale, P. M. ; Jacobs , H. S. ; and James , V.H.T.

(1982) : Salivary testosterone : Relationship to unbound plasma testosterone in normal and hyper - androgenic women. Clin. Endocrinol., 16 , 595.

- Baxendale, P. M. ; Jacobs , H. S. ; and James, V.H.T.
(1983) : Plasma and Salivary andro
Stendione and dihydrotestosterone in
women with hyper androgenism. Clin.
Endocrinol., 18 , 447.
- Bibbo, M. ; Gill, W.B. ; Aziz , F. ; Blough, R. ; Fang,
V.S. ; Rosenfield ,R. L. ; Schumacher,
G. F. ; Sleper , K. M.; Sonek , M. ;
and Wied , G. L. (1977) : Follow up
study of male and female offspring
of DES exposed mothers. Obstet.
Gynaecol., 49 , 1.
- Blankstein , J. ; Fariman , C. ; Reyes F. I. ; et al.
(1980) : Adult - Onset familial adrenal
21 - hydroxylase deficiency. Am. J. Med.,
68 , 441.
- Blum , I.; Kaufman , H.; Marilus , R. ; et al. (1981) :
Successful treatment of polycystic ovary
syndrome with spironolactone. Obstet.
Gynaecol., 57 , 661.
- Boisselle , A. ; and Tremblay , R. R. (1979) :
New therapeutic approach to the hirsute
patient. Fertil. Steril., 32 , 276.

Bolte , E.; Coudert , S. ; and Lefebvre , Y. (1974) :

Steroid production from plasma cholesterol. II : In vivo conversion of plasma cholesterol to ovarian progesterone and adrenal C₁₉ and C₂₁-Steroids in human. J. Clin. Endocrinol. Metab., 38 , 394.

Braithwaite , S.S. ; Erkman - Balis, B.; and Avila , T.D. (1978) : Postmenopausal virilization due to ovarian stromal hyperthecosis. J. Clin. Endocrinol. Metab., 46 , 295.

Braithwaite , S.S. ; and Jabamoni , R. (1983) :
Hirsutism. Arch. Dermatol., 119 , 279.

Burchardt , P. ; and Agrapidakis , J. (1972) :
Quoted by Dewhurst, C. J. , et al 1977.
The treatment of hirsutism with cyproterone acetate (an anti androgen).
Br. J. of Obstet. and Gynaecol. ,
84 , 119.

Buvat , J. ; Siame - Mourot , C. ; Four linnie , J. C.

Lemaire , A. ; Buvat - Herbaut , M. ;
and Hermand , E. (1982) : Androgens
and prolactin levels in hirsute women
with either poly cystic ovaries or,
" border line ovaries ". Fertil.
Steril., 38 , 695.

Childs , B. ; Grumbach , M. M. ; and Van Wyk , J.J.

(1956) : Virilizing adrenal hyperplasia :
a genetic and hormonal study. J. Clin.
Invest., 35 , 213.

Chrousos , G. P. ; Loriaux , D. L. ; Mann , D. L. ; et al.

(1982) : Late - onset 21 - hydroxylase
deficiency mimicking idiopathic hirsutism
or polycystic ovarian disease. Ann.
Intern. Med. , 96 , 143.

Clark , A. F. ; and Bird , C. E. (1973) : Binding of

5 α - androstane- 3 α , 17 B-diol to
human plasma proteins. J. Endocrinol.,
57 , 289.

Correa de Oliveira , R. F. ; Novaes , L. P. ; Lima ,

M. B. ; et al. (1975): A new treatment
for hirsutism. Annals of Intern.
Med., 83 , 817.

Covol , P. L. ; Chrambach , A. ; Rodbard , D. ; and
Bardin, C. W. (1971) : Physical
properties and binding capacity of
testosterone extradiol Binding
globulin in human plasma determined
by polyacry lamide gel electro-
phoresis. J. Biol. Chem., 246 , 3435.

Corvol , P. ; M ; Chaud , A. ; Menard , J. ; et al.
(1975) : Anti - androgenic effect of
spironolactone : Mechanism of action.
Endocrinology , 97 , 52.

Coulam , C; B. (1974) : The hirsute person :
A commentary. Med. Clin. , N. Am.
J. 58 , 877.

Cumming , D. C. ; Yang , J. C. ; Rebar , R. W. ; et al.
(1982) : Treatment of hirsutism with
Spironolactone. Jama , 247 , 1295.

De lange , W. E. ; Pratt , J. J. ; and Doorenbos, H.

(1980) : A gonado trophin responsive testosterone producing adrenocortical adenoma and high gonadotrophin levels in an elderly woman. Clin. Endocrinol., 12 , 21.

Dew hurst , C. J. ; Underhill ,R. ; Goldman, S. ; and

Mansfield, M. (1977) : The treatment of hirsutism with Cyproterone acetate (an antiandrogen). Br. J. of Obstet- and Gynaecol., 84 , 119.

Dieckmann, W. J. ; Davis , M.E. ; Rynkiewicz, L. M. ;

et al. (1953): Does the administration of diethylstilbesterol during pregnancy have therapeutic value ? Am. J. Obstet. Gynaecol., 66 , 1062

Domonkos, A. N.; Arnold, H. L. ; and Odom , R.B. (1982) :

Andrew's Diseases of the skin. Clinical Dermatology 7th edn. Chap. 32. Philadelphia. W.B. Saunders Company. P , 953.

Easterling, W. E. ; Talbert , L.M. ; and Potter, H.D. (1974):

Serum testosterone levels in the polycystic ovary syndrome. Am. J. Obstet. Gynaecol., 120 , 385.

Ebling , F. J. ; Rook , A. (1972) : In Text book of Dermatology 2nd edn. Rook , A. ; Wilkinson, D. S. ; and Ebling , F. J. (Eds). Blackwell Scientific Publications. Oxford. p , 1559.

Ebling , F. J. ; Thomas , A. K. ; Cooke , I. D. ; Randall , V. A. ; Skinner , J. ; and Cawood , M. (1977) : Effect of cyproterone acetate on hair growth, sebaceous secretion and endocrine parameters in a hirsute subject Br. J. Dermatol., 97 , 371.

Ebling , F. J. ; and Rook, A. (1979) : Hair In textbook of Dermatology. 3rd edn. Rook, A. , Wilkinson, D.S. , and Ebling , F. J. (Eds). Blackwell scientific publications Oxford. p, 1757.

Elert , A. (1969) : Quoted by Dewhurst, C.J. , et al 1977. The treatment of hirsutism with cyproterone acetate (an antiandrogen). Br. J. of Obstet. and Gynaecol., 84 , 119.

- Farber, M. ; Millan, V.G. ; Turksoy, R. N. , et al. (1978):
Diagnostic evaluation of hirsutism in
women by selective adrenal and
ovarian venous catheterization. Fertil.
Steril., 30 , 283.
- Fayez , J. A. ; Bunch , T. R. ; and Miller , G. L. (1974) :
Virilization in pregnancy associated with
an ovarian cystadenoma Am. J. of Obstet
and Gynaecol. , 120 , 341.
- Ferriman, D. ; and Galloway, J. D. (1961) : Clinical
assessment of body hair growth in women
J. Clin. Endocrinol., Metab. , 21 , 1440.
- Ferriman, D. ; et al. (1962) : Studies bearing on the
nature of andrology. J. Endocrinol.,
25 , 351.
- Flamigni, C. ; Collins, W. P. ; Koullapis, E. N. ; et al.
(1971) : Androgen metabolism in human
skin. J. Clin. Endocrinol Metab.,
32 , 737.
- Fleet wood, J. A.; Leigh., R.J. ; Hall, R. ; et al. (1974) :
Evidence for an underlying adrenocortical
abnormality in hirsute women. Clin.
Endocrinol., 3, 457.

- Frey, H.; and Aakvaag, A. (1981) : The treatment of essential hirsutism in women with cyproterone acetate and ethinyl estradiol. Acta Obstet. Gynaecol. Scand., 60 , 295.
- Frohlich, M. ; Vader, H. L.; Valma, S.T. ; and deRooy, H.A.M. (1980) : The influence of long term treatment with cyproterone acetate or a cyproterone acetate - ethinyl estradiol combination on androgen levels in blood of hirsute women. J. Steroid. Biochem., 12, 499.
- Fuller, P. J.; Pettigrew, I.G. ; Pike, J.W. ; and Stockigt, J.R. (1983) : An adrenal adenoma causing virilization of mother and infant. Clin. Endocrinol. , 18 , 143.
- Garn, S. M. (1981) : Types and distribution of the hair in man. Ann. N.Y. Acad. Sci. , 53 , 498.
- Girard, J. ; Baumann, J.B. ; Buhler, U.; Zuppinger, K. ; Haas, H. G. ; Staub, J. J. ; and Wyss, H. I. (1978) : Cyproterone acetate and ACTH adrenal function, J. Clin. Endocrinol. Metab., 47, 581.

Givens, J.R. ; Wiser, W.L.; Coleman, S.A.; Wilroy, R.S.;
Anderson, R.N.; and Fish, S.A. (1971) :
Familial ovarian hyperthecosis : A study
of two families. Am. J. Obstet. Gynaecol.,
110 , 959.

Givens, J.R.; Anderson, R.N.; Wiser, W.L.; Coleman, S.A.;
and Fish, S.A. (1974) : A gonadotropin-
responsive adrenocortical adenoma.
J. Clin. Endocrinol. Metab., 38, 126.

Givens, J.R. ; Anderson R.N.; Ragland, J.B; Wiser, W.L.;
and Umstot, E.S. (1975) : Adrenal function
in hirsutism : 1- Diurnal charge and
response of plasma androstenedione,
testosterone, 17 hydroxy progesterone,
Cortisol, LH and FSH to dexamethasone
and $\frac{1}{2}$ unit of ACTH. J. Clin. Endocrinol.
Metab., 40 , 988.

Givens, J.R. ; Anderson, R.N. ; Wiser, W.L. ; Umstot,
E. S. ; and Fish, S.A. (1976) : The
effectiveness of two oral contraceptives
in suppressing plasma androstenedione,
testosterone, LH and FSH, and in stimulating
plasma testosterone - binding capacity in
hirsute women. Am. J. Obstet. Gynaecol.,
15 , 333.

- Givens, J.R. (1976) : Hirsutism and hyperandrogenism.
Adv. Intern. Med., 21 , 221.
- Gold, J.J. (1975) : Hirsutism and Virilism. In
Gynaecologic endocrinology 2nd edn.
Harper and Row publisher. New York.
p , 448.
- Goldzieher, M. W. ; and Green, J. A. (1962) : The polycystic
ovary I. clinical and histological features,
J. Clin. Endocrinol. Metab., 22 , 235.
- Gordon, G.G.; Southren, A.L. ; Tochimoto, S. ; et al.
(1970) : Effect of medroxy progesterone
acetate (Provera) on the metabolism and
biological activity of testosterone.
J. Clin. Endocrinol., 30 , 449
- Greenblatt, R.B. (1953) : Cortisone intreatment of
hirsute woman. Am. J. Obstet. Gynaecol.,
66, 700.
- Greenblatt, R.B. (1963) : The hirsute female. Charles,
C. Thomas, Springfield Illinois ,
U.S.A.

Gupta , D.; Rager, K.; Huenges , R. ; and Bierich , J.R.

(1975) : Urinary anrogen response of eight girls with precocious puberty given cyproterone acetate Endocrinol., 65 , 138.

Guthrie, G.P. Jr.; Wilson , E.A. ; Quillen, D.L. ; and

Jawad , M.J. (1982) : Adrenal androgen excess and defective 11 B-hydroxylation in women with idiopathic hirsutism. Arch. Intern. Med., 142 , 729.

Hamada, H. ; Newmann, F.; and Junkman. (1963) : Quoted

by Dewhurst C.J.; et al., 1977., The treatment of hirsutism with cyproterone acetate (an anti-androgen). Br. J. Obstet. Gynaecol., 84, 119.

Hamilton, J.B.; and Terada, H. (1963) : In the hirsute

female. Ed. Greenblatt, R.S. Springfield Thomas, p. 20.

Hammerstein, J. ; and Cupceancu, B. (1969) : Quoted by

Dewhurst, C.J. ; et al., 1977., The treatment of hirsutism with cyproterone acetate (an antiandrogen). Br. J. Obstet. Gynaecol., 84 , 119.

- Haney, A.F. ; Hammond, C.B.; Soules, M.R.; and Creasman, W.T. (1979) : Diethylstilbesterol - induced upper genital tract abnormality. Fertil. Steril., 31 , 142.
- Haris, H. (1947) : The relation of hair growth on the body to baldness. Br. J. Dermatol. Syph., 59 , 300.
- Hatch, R.; Rosenfield , R.L; Kim, M.H.; et al. (1981) : Hirsutism : Implications, etiology, and management. Am. J. Obstet. Gynaecol., 140 , 815.
- Hay, J.B.; and Hodgins, M.B. (1978) : Distribution of androgen metabolizing enzymes in isolated tissues of human forehead and axillary skin, J. Endocrinol., 79 , 29.
- Herbst, A.L.; Ulfelder, H. ; and Poskanzer, D.C. (1971) : Adenocarcinoma of the vagina : Association of maternal stilbesterol therapy with tumour appearance in young women. N. Engl. J. Med., 284 , 878.

- Horton, R. ; and Neisler, J. (1969) : Plasma androgen in patients with the polycystic ovary syndrome. J. Clin. Endocrinol., 28 , 479.
- Horton, R. ; Hawks, D.; and Lobo, R. (1982) : 3 - α , 17-B - androstenediol glucuronide in plasma : A marker of androgen action in idiopathic hirsutism. J. Clin. Invest., 69, 1203.
- HoYuen, B.; and Mincey, E.K. (1983) : Role of androgen in menstrual disorders of non hirsute and hirsute women, and the effect of glucocorticoid therapy on androgen levels in hirsute hyperandrogenic women. Am. J. Obstet. Gynaecol., 145 , 152.
- Inaudi, P.; D'Ambrogio, G. ; Massafra, C. ; Facchini, V.; and Genazzani, AR. (1982) : Impaired pregnenolone secretion after combined cyproterone acetate and ethinyl estradiol therapy in hirsute patients. Gynaecol. Obstet. Invest. , 14 , 106.

- Ismail , A.A.A. ; Davidson, D.W. ; Sonka, A.R. ; et al.
(1974) : The evaluation of the role
of androgen in hirsutism and the use
of a new anti-androgen cyproterone
acetate for therapy. J. Clin. Endocrinol.
Metab., 39 , 81.
- Ito , T. ; and Horton , R. (1970) : Dihydrotestosterone in
human peripheral plasma. J. Clin.
Endocrinol. Metab., 31 , 362.
- Jones, K.R. ; Katz, M.; Keyzer, C.; et al. (1981) :
Effect of cyproterone acetate on rate
of hair growth in hirsute females.
Br. J. Dermatol., 105 , 685.
- Judd, H. L. ; McPherson, R.A. ; Rekoff, J.S ; and Yen,
S.S.C. (1977) : Correlation of the
effects of dexamethasone administration
on urinary 17 ketosteroid and serum
adrogen levels in patients with hirsutism.
Am. J. Obstet. Gynaecol., 128 , 408.
- Kem, D.C.; Gomez - Sanchez, C.; Kramer, N.J.; et al. (1975):
Plasma aldosterone and renin activity
response to ACTH infusion in dexamethasone
suppressed normal and sodium - depleted
man. J. Clin. Endocrinol. Metab., 40, 116.

- Kirschner, M.A. ; Bardin, C.W. ; Hembree, W.C. ; and
Ross, G.T. (1970) : Effect of estrogen
administration on androgen production
and plasma luteinizing hormone in
hirsute women. J. Clin. Endocrinol.
Metab., 30 , 727.
- Kirschner, M.A. ; and Jacobs, J.B. (1971) : Combined
ovarian and adrenal vein catheterization
to determine the sites of androgen
over production in hirsute women. J.
Clin. Endocrinol., 33 , 199.
- Kirschner, M.A.; Sinhamahapatra, S. ; Zucker, I.R. ;
Loriaux, L.; and Nieschlag, E. (1973) :
The production, origin and role of
dehydroepiandrosterone and D⁵-
androstenediol as androgen prehormones
in hirsute women. J. Clin. Endocrinol.
Metab., 37 , 183.
- Kirschner, M.A.; Zucker, I.R. ; and Jespersen, D. (1976) :
Idiopathic hirsutism : An ovarian
abnormality. N. Engl. J. Med., 294 , 637.

- Lachelin, G.C.L. ; Judd, H.L. ; Swanson, S.C. ; Hauck, M.E. ; Parker, D.C. ; and Yen, S.S.C. (1982) : Long term effects of nightly dexamethasone administration in patients with polycystic ovarian disease. J. Clin. Endocrinol. Metab. , 55 , 768.
- Larson, B.A. ; Vanderlaan, W.P. ; Judd, H.L. ; and McCullough, D.L. (1976): A testosterone producing adrenal cortical adenoma in an elderly woman. J. of Clin. End. and Metab., 42 , 882.
- Lloyd, C.W. ; et al. (1963) : Studies of adrenocortical function of women with idiopathic hirsutism: response to 25 units of ACTH. J. Clin. Endocrinol. Metab. , 23 , 413.
- Lunell, N.O. ; Zador, G.; Carlstrom, K. Eneroth, P. ; Patek , E. ; and Wager , J. (1982) : The effect of cyproterone acetate on pituitary-ovarian function and clinical symptoms in hirsute women. Acta Endocrinol., 100 , 91 .

- Mahesh , V.B. ; and Greenblatt, R.B. (1962) : Isolation of dehydroepiandrosterone and 17α - hydroxypregnenolone from the polycystic ovaries of the Stein-Leventhal syndrome. J. Clin. Endocrinol. Metab., 22 , 441.
- Mahesh, V.B. ; Green blatt, R.B. ; and Coniff, R.F. (1968) : Urinary steroid excretion before and after dexamethasone administration , and steroid content of adrenal tissue and venous blood in virilizing adrenal tumours. Am. J. Obstet. Gynaecol., 100 , 1043.
- Mahoudeau, J. A. ; Bardin, C.W. ; and Lipsett , M. B. (1971) : The metabolic clearance rate and origin of plasma dihydrotestosterone in man and its conversion to the 5α - androstenediols. J. Clin. Invest., 50 , 1338.
- Maroulis, G.B. ; Maulimos, F.S. ; and Abraham , G. E. (1977) : Comparison between urinary 17 - ketosteroids and serum androgens in hirsute patients. Obstet. Gynaecol. , 49 , 454.

- Mauvis - Jarvis, P. ; Charansol, G. , and Masson, F.B.
(1973) : Simultaneous determination of urinary androstenediol and testosterone as an evaluation of human androgenicity. J. Clin. Endocrinol. Metab., 36 , 452.
- Mc-Knight, E. (1964) : The prevalence of hirsutism in young women. Lancet, 1, 410.
- Mc-Natty, K.P. ; Makris, A.; DeGrazia, C. ; Osathanondh, R. ; and Ryan, K.J. (1979) : The production of progesterone, androgens and estrogens by granulosa cells, theca tissue and stromal tissue from human ovaries in vitro. J. Clin. Endocrinol. Metab., 49 , 687.
- Meikle, A. ; Stringham, J. ; Wilson , D. ; and Dolman, L.
(1979) : Plasma 5 α - reduced androgens in men and hirsute women : role of adrenals and gonads. J. Clin. Endocrinol. Metab. , 48 , 969.
- Menard, R.H. ; Stripp, B.; and Gillette, J.R. (1974) :
Spironolactone and testicular cytochrome : Decreased testosterone formation in several species and changes in hepatic drug metabolism. Endocrinology., 94 , 1628.

Moll, G. W. , Jr. ; and Rosenfield, R. L. (1979) :

Testosterone binding and free plasma androgen concentration under physiological conditions : Characterization of flow dialysis technique. J. Clin. Endocrinol. Metab., 49 , 730.

Murset, G. ; Zachmann, M. ; Prader, A. ; Fischer, J. ;

and Labhart, A. (1970) : Male external genitalia of a girl caused by a virilizing adrenal tumour in the mother. Acto Endocrinol. , 65, 627.

Neumann, F. (1971) : Quoted by Dewhurst, C. J. , et al.,

1977. The treatment of hirsutism with cyproterone acetate (an antiandrogen). Br. J. Obstet. Gynaecol., 84 , 119.

New, M. I. ; Lorenzen, F. ; Pang, S. ; Gunczler, P. ;

DuPout, B. ; and Levine , L. S. (1979) : " Acquired " adrenal hyperplasia with 21 - hydroxylase deficiency is not the same genetic disorder as congenital adrenal hyperplasia. J. Clin. Endocrinol. Metab., 48 , 356.

- Newmark, S. ; Dluhy, R.G. ; Williams , G. H. ; Pochi ,
P. ; and Rose, L.I. (1977) : Partial
11 - and 21 - hydroxylase deficiencies
in hirsute women. Am. J. Obstet.
Gynaecol., 127 , 594.
- Novak , E.R. ; and Long, J.H. (1965) : Arrhenoblastoma
of the ovary. Am. J. Obstet. Gynaecol.,
92 , 1082.
- Ober, K. P. ; and Hennessy , J. F. (1978) : Spironolactone
therapy for hirsutism in hyperandrogenic
woman. Ann. Intern. Med. , 89 , 643.
- O'Connor , S. ; Baker, H.W.G. ; Dulmanis, A.; and Hudson,
B. (1973) : The measurement of sex
steroid binding globulin by differential
ammonium sulphate precipitation. J. Steroid
Biochem., 4 , 331.
- Parker, C. R. , Jr. ; Bruneteau, D.W. ; Greenblatt , R. ;
and Mahesh, V. B. (1975) : Peripheral ,
ovarian and adrenal vein steroids in hirsute
women : acute effects of human chorionic
gonadotropin and on adrenocortico trophic
hormone. Fertil. Steril. , 26 , 877.

Paulson, J. ; Keller, D. ; Wiest, W. ; and Warren, J.

(1977) : Free testosterone concentration in serum : elevation is the hallmark of hirsutism. Am. J. Obstet. Gynecol. , 128 , 851.

Peress , M.R. ; Tsai, C.C. ; Mathur, R.S. ; and Williamson,

H.O. (1982) : Hirsutism and menstrual patterns in women exposed to diethylstilbesterol in utero. Am. J. Obstet. Gynaecol., 144 , 135.

Polansky, S. ; dePapp, E.W. ; and Ogden, E.B. (1975) :

Virilization associated with bilateral luteomas of pregnancy. Obstet. and Gynaecol., 45 , 516.

Rasmusson, G. H. ; Chen, A. ; Reynolds, G. F. ; Patanelli,

D.J. ; patchett, A.A. ; Arth, G.E. (1972) : Quoted by Corvol, P., et al 1975 .

Antiandrogenic effect of spironolactone : Mechanism of action. Endocrinology , 97 , 52.

- Rebar, R. ; Judd, H. L. ; Yen, S.S.C. ; Rakoff, J. ;
Vandenberg , G. ; and Naftolin , F.
(1976) : Characterization of the
inappropriate gonadotropin secretion
in polycystic ovary syndrome. J.
Clin. Invest. , 57 , 1320.
- Rich, B. H. ; Rosenfield, R. L. ; Lucky, A.W. ; et al.
(1981) Adrenarche : changing adrenal
response to ACTH. J. Clin. Endocrinol.
Metab., 52 , 1129.
- Riddick, D.H. ; and Hammond, C.B. (1975) : Adrenal
Virilism due to 21 - hydroxylase
deficiency in the postmenarchia female.
Obstet. Gynaecol. , 45 , 21.
- Rifka , S.M. ; Pita, J.C. ; Vigersky, R.A. ; et al.(1978):
Interaction of digitalis and spironolactone
with human sex steroid receptors. J.
Clin. Endocrinal. Metab., 46 , 338.
- Rose, L.I. ; Underwood, R.H. ; New mark, S. R. ; et al.
(1977) : pathophysiology of spironolactone-
induced Gynecomastia. Ann. Intern. Med.,
87 , 398.

Rosenfield, R. L. (1971) : Plasma testosterone binding globulin and indexes of the concentration of unbound plasma androgen in normal and hirsute subjects. J.Clin. Endocrinol., 32 , 717.

Rosenfield, R.L.; Ehrlich , E.N. ; and Cleary, R.E. (1972): Adrenal and ovarian contribution to the elevated free plasma androgen levels in hirsute women. J. Clin. Endocrinol., 34 , 92.

Rosenfield, R.L. (1972) : Role of androgens in growth and development of the fetus, child and adolescent. Adv. Pediat., 19, 171.

Rosenfield, R.L. (1975) : Studies of the reaction of plasma androgen levels to androgen action in women. J. Steroid Biochem., 6 , 695.

Rosenfield, R.L. (1976) : Letter to the editor. N. Engl. J. Med., 295 , 232.

- Rosenfield , R. L. ; Rich, B.H. ; Wolfsdorf, J.I.; et al.
(1980) : Pubertal presentation of
congenital D⁵- β - B - hydroxysteroid
dehydrogenase deficiency. J. Clin.
Endocrinol. Metab., 51 , 345.
- Rosenwaks, Z. ; Lee, P.A. ; Jones, G. S. ; Migeon, C.J. ;
and Wentz, A. , C. (1979) : An attenuated
form of congenital virilizing adrenal
hyperplasia. J. Clin. Endocrinol. Metab.,
49 , 335.
- Rosner, W. (1972) : A simplified method for the quantitative
determination of testosterone - estradiol
binding globulin in human plasma. J. Clin.
Endocrinol. Metab., 34 , 983.
- Schmidt, G.; Fowler, W.C. ; Talbert, L.M. ; and Edelman,
D., A. (1980) : Reproductive history of
of women exposed to diethylstilbesterol
in utero. Fertil. Steril., 33, 21.
- Schweikert, H.U.; and Wilson, J.D. (1974,a) : Regulation
of human hair growth by steroid hormones.
I. Testosterone metabolism in isolated
hairs. J. Clin. Endocrinol. Metab.,
38 , 811.

Schweikert , H. U. ; and Wilson, J. D. (1974 , b) :

Regulation of human hair growth by steroid hormones. II. Androstenedione metabolism in isolated hairs. J. Clin. Endocrinol. Metab., 39 , 1012.

Shapiro , A.V. ; and Evron, S. (1980) : A novel use of spironolactone : Treatment of hirsutism. J. Clin. Endocrinol. Metab., 51 , 429.

Sharp, F. ; Hay, J.B. ; and Hodgins, M.B. (1976) :

Metabolism of androgens in vitro by human fetal skin. J. of Endocrinol, 70 , 491.

Smals, A.G. H.; Kloppenborg , P.W.C. ; Goverde, H.J.M.; and Benraad, Th. J. (1978) : The effect of cyproterone acetate on the pituitary adrenal axis in hirsute women. Acta Endocrinol., 87 , 352.

Smith , R.G. ; Besch, P.K. ; Dill, B.; and Buttram, V.C.

Jr. (1979) : Saliva as a matrix for measuring free androgens : Comparison with serum androgens in polycystic ovary disease. Fertil. Steril., 31 , 513.

- vanWayjen, R. G. A. ; and van den Ende, A. (1981) :
Effect of cyproterone acetate on
pituitary - adrenocortical function in
man. *Acta. Endocrinol.*, 96 , 112.
- Verhoeven, A.T.M. ; Mastboom, J.L. ; Vanleusden, H.A.I.M. ;
and Van der Velden, W.H.M. (1973) :
Virilization in pregnancy coexisting with
an ovarian mucinous cystadenoma ; a case
report and review of virilizing ovarian
tumours in pregnancy. *Obstet. and
Gynaecol. Survey.*, 28 , 597.
- Verkauf , B.S. ; Reiter, E.O. ; Hernander, L. ; and
Burns, S.A. (1977) : Virilization of
mother and fetus associated with
luteoma of pregnancy : a case report
with endocrinologic studies. *Am. J.
of Obstet. & Gynaecol.*, 129 , 274.
- Vermeulen, A. ; Verdonch, L. ; Van-Straeten, M. ; and
Orie, N. (1969) : Capacity of testosterone
globulin in human plasma and influence
of specific binding testosterone in its
metabolic clearance rate. *J. Clin.
Endocrinol. Metab.*, 29 , 1470.

Vermeulen, A. ; Stoica, T.; and Verdonch , L. (1971) :

The apparent free testosterone
concentration : An index of androgenicity.
J. Clin. Endocrinol. Metab., 33 , 759.

Voigt, K.L.; Apostalakis, M. ; and Tamm, J. (1968) :

Advances in the Biosciences, 3.
Workshop on Steroid Metabolism " In
Vitro Versus In Vivo." Schering Berlin,
p , 185.

Voigt, W. ; Fernandez ,E.P. ; and Hsia , S.L. (1970) :

Transformation of testosterone into
17 B- hydroxy 5 α - androstan - 3 - one
by microsomal preparations of human
skin. J. Biol. Chem., 245 , 5544.

Vokaer, R. ; and Kridelka, J. C. (1963) : Quoted by

Dewhurst, C. J. , et al.1977. The
treatment of hirsutism with cyproterone
acetate (an antiandrogen). Br. J. of
Obstet. and Gynaecol., 84 , 119.

Wartsman, J. ; Singh, K. B.; and Murphy, J. (1981) :

Evidence for the hypothalamic origin of
the polycystic ovary syndrome. Obstet.
Gynaecol., 58 , 137.

- Weist, W. G. ; Paulson, J. D. ; Keller, D. W. ; and
Warren, J. C. (1978) : Free testosterone concentration in serum : a method for determination. Am. J. Obstet. Gynaecol., 130 , 321.
- Wilson, J. D. (1972) : Recent studies on the mechanism of action of testosterone. N. Engl. J. Med., 287 , 1284.
- Wn, C. H. ; Mangan. C.E. ; Burtnett, M . M. ; and
Mikhail , G. (1980) : Plasma hormones in DES - exposed females. Obstet. Gynaecol., 55 , 157.
- Zielske, F. ; Leo-Rossberg, I. ; Drey-Kluft, R. ; Rommler, A. ; and Hammerstein, J. (1971) : Treatment of hirsutism and other signs of virilism with a reversed sequential administration of cyproterone acetate and ethinyl estradiol, clinical and endocrinal aspects. Acta. Endocrinol., 67 , Suppl. 155 , 172.