HYPERANDROGENISM AND ANDROGEN EXCESS

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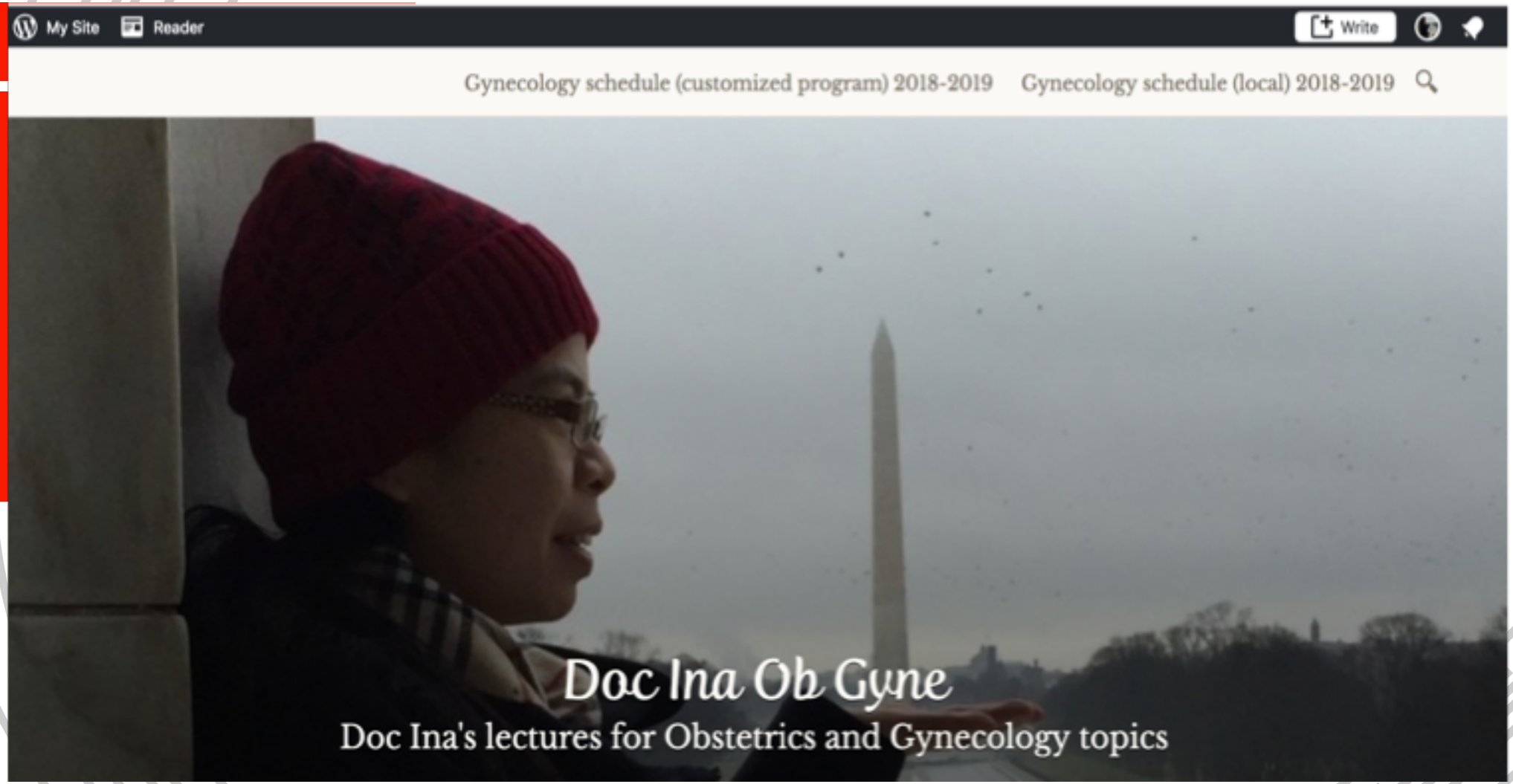


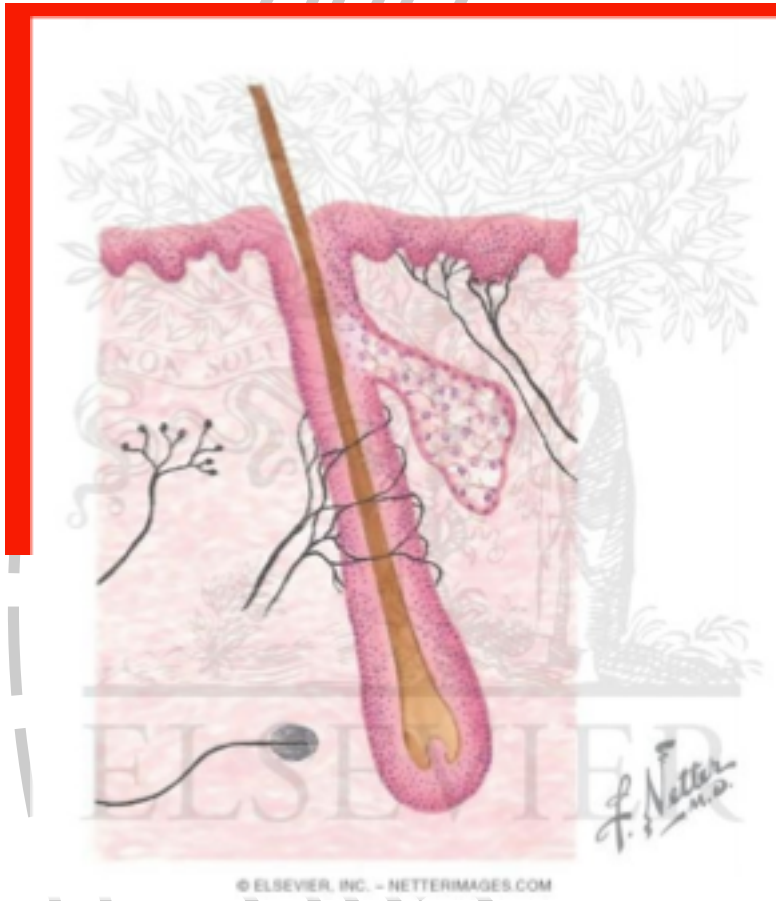
Reference

- Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 40, Hyperandrogenism and androgen excess

Outline

- Review of Pilosebaceous unit
- Physiology of androgens in women
- Causes of hyperandrogenism
- Treatment

REVIEW: Pilosebaceous unit



- the PSU is composed of a sebaceous component and pilary component from which the hair shaft arises.
- Abnormalities of the sebaceous component lead to acne, and abnormalities of the pilary unit lead to excessive growth (hirsutism) or excessive shedding (alopecia).
- there are two types of hair:
  - vellus hair is soft, fine, and unpigmented
  - terminal hair is coarse, thick, pigmented, and undergoes cyclic changes.
- Anagen is the growth phase of hair. It is followed by the transitional catagen phase and, finally, by a resting, or telogen, phase, after which the hair sheds
- Androgen is necessary to produce development of terminal hair
- duration of anagen also determines the length of hair, which varies in different parts of the body. For facial hair it is approximately 4 months, which has implications for the treatment of facial hirsutism

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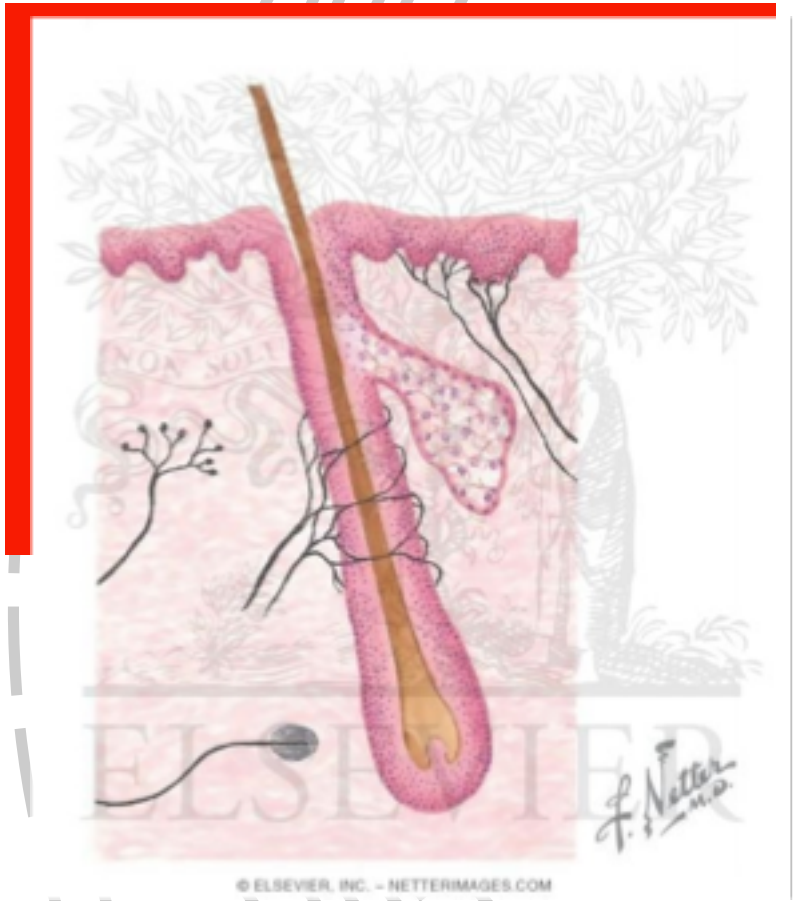
REVIEW: Pilosebaceous unit



- there are several steroidogenic enzymes in the hair follicle, but the activity level of the enzyme **5α-reductase** most directly influences the degree of androgenic effect on hair growth.
- With elevated levels of circulating androgen or increased activity of 5α-reductase, terminal hair appears where normally only vellus hair is present.
- With these alterations, the length of the anagen phase is prolonged and the hair becomes thicker.
- Excessive 5α-reductase activity also may lead to acne as well as scalp hair loss (alopecia).

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Modified Ferriman Gallwey scoring system for hirsutism

- the presence of hirsutism without other signs of virilization is associated with a milder increase in androgenic activity, compared to what is observed with virilization, and it has a longer, more gradual onset.
- In the milder forms of hirsutism, hair is found only on the upper lip and chin
- Severe hirsutism involves hair growth on the cheeks, chest (intermammary), abdomen (superior to the umbilicus), inner aspects of the thighs, lower back, and intergluteal areas.
- the severity of the hirsutism can be roughly quantified by a modified scoring system of Ferriman and Gallwey (MFG)

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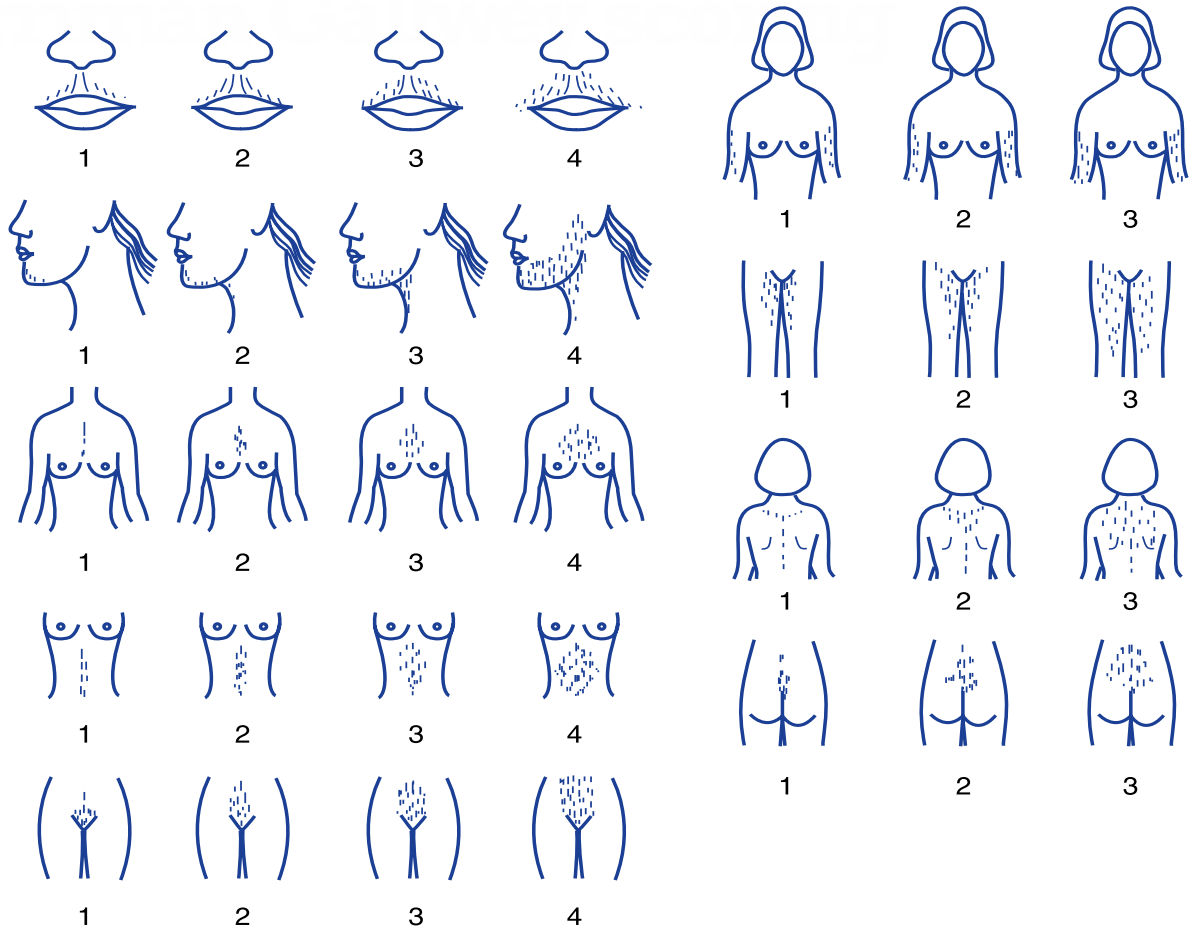
Modified Ferriman Gallwey scoring system for hirsutism



<6-8 normal 8-15 mild hirsutism >15 moderate to severe hirsutism

Witchela SF, Oberfieldb S, Rosenfield RL, Codnerd E, Bonnye A, Ibáñezf L, Penag A, Horikawah R, Gomez-Loboi V, Joelj D, Tfaylik H, Arslanianl S, Dabadghaom P, Garcia C, Rudazn,Lee PA.The Diagnosis of Polycystic Ovary Syndrome during Adolescence. Horm Res Paediatr 2015;83:376–389 DOI: 10.1159/000375530

Modified Ferriman Gallwey scoring system for hirsutism

- A score greater than 6 or 8 has generally been considered to be consistent with hirsutism
- In Asian women the threshold for an abnormal score is much lower at >3

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Hypertrichosis; virilization

- Increased hair growth only on the extremities or in isolated areas is called **hypertrichosis** and should not be confused with hirsutism.
- **Virilization** is a relatively uncommon clinical finding and its presence is usually associated with markedly elevated levels of circulating testosterone (≥2 ng/mL).
  - signs of virilization usually occur over a relatively short period.
  - these signs are caused by the masculinizing and defeminizing (antiestrogenic) actions of testosterone and include temporal balding, clitoral hypertrophy, decreased breast size, dryness of the vagina, and increased muscle mass.

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PHYSIOLOGY OF ANDROGENS IN WOMEN

- major androgen produced by the ovaries is **testosterone** (0.1 mg/day)
  - Other androgens secreted by the ovary are androstenedione (1 to 2 mg/day) and DHEA (<1 mg/day).
- major androgen produced by the adrenal glands is **dehydroepiandrosterone sulfate (DHEAS)** (6-14 mg/day)
  - Other androgens secreted by the ovary are androstenedione (1 mg/day) and DHEA (1 mg/day).
  - normal adrenal gland secretes little testosterone
- conversion of androstenedione and Dehydroepiandrosterone (DHEA) to testosterone occurs in peripheral tissues.

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PHYSIOLOGY OF ANDROGENS IN WOMEN

- **Androstenedione and DHEA do not have strong androgenic activity** but are peripherally converted at a slow rate to the biologically active androgen, **testosterone.**
- Only approximately 5% of androstenedione and a smaller percentage of DHEA are converted to testosterone. e total daily production of testosterone in women is normally approximately 0.35 mg.

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PHYSIOLOGY OF ANDROGENS IN WOMEN

- Most testosterone in the circulation (≈85%) is tightly bound to sex hormone-binding globulin (SHBG) and is believed to be biologically inactive.
- An additional 10% to 15% is loosely bound to albumin, with only approximately 1% to 2% not bound to any protein (**free testosterone**).
- Both the free and albumin-bound testosterone (*unbound testosterone*) are biologically active.

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PHYSIOLOGY OF ANDROGENS IN WOMEN

- To exert a biologic effect, testosterone is metabolized peripherally in target tissues to the more potent androgen **5α-dihydrotestosterone (DHT)** by the enzyme **5α- reductase**.
- 5α-reductase activity is important for testosterone action peripherally (pilosebaceous unit) as well as in the genitalia.
- **5α-androstane-3α,17β-diol glucuronide (3α-diol-G)**, is a stable, irreversible product of intracellular 5α-reductase activity and reflects this activity in blood

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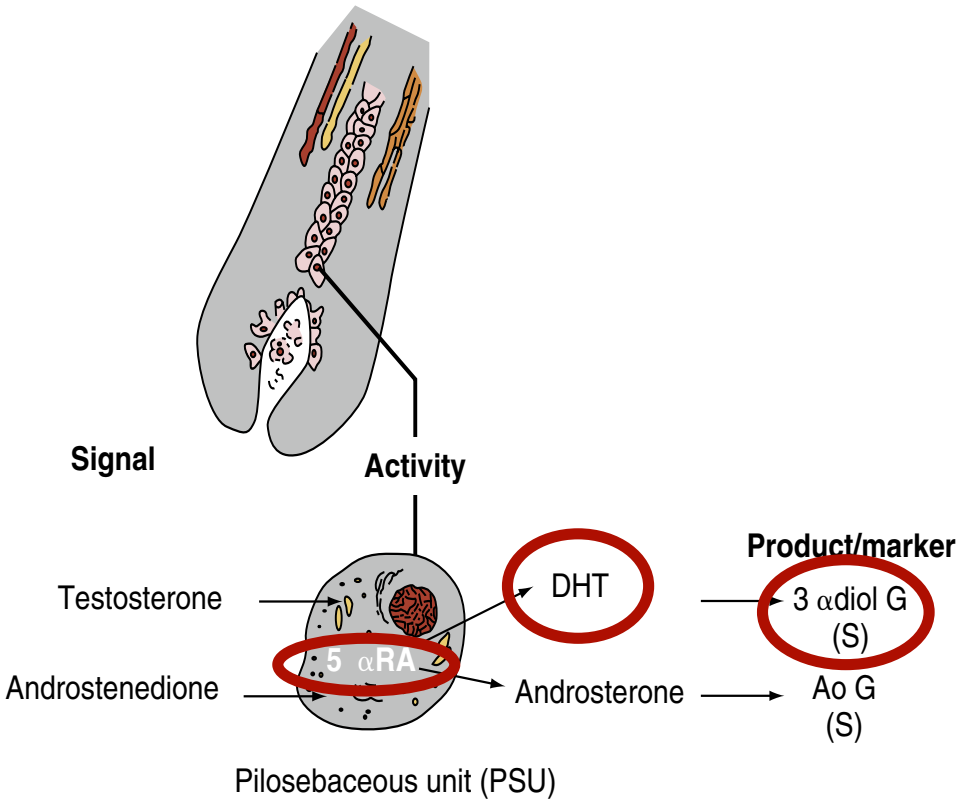

Figure 40.3 Peripheral androgen metabolism and markers of this activity. *Ao G*, Androsterone glucuronide; *DHT*, dihydrotestosterone; 3 αdiol G, 3α-androstanediol glucuronide; *(S)*, serum. (From Lobo RA. Androgen excess. In: Mishell DR Jr, Davajan V, Lobo RA, eds. *Infertility, Contraception and Reproductive Endocrinology.* 3rd ed. Cambridge, MA: Blackwell Scientific; 1991.)

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PHYSIOLOGY OF ANDROGENS IN WOMEN

- Even with normal circulatory levels of androgen, increased 5α-reductase activity in the PSU results in increased androgenic activity, producing hirsutism
- degree of 5α-reductase activity can be measured in skin biopsies;
- if necessary for diagnostic reasons, **3α-diol-G** levels can be directly measured in serum → measurement of this metabolite is the **most accurate indicator of the degree of peripheral androgen metabolism in women.**

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PHYSIOLOGY OF ANDROGENS IN WOMEN

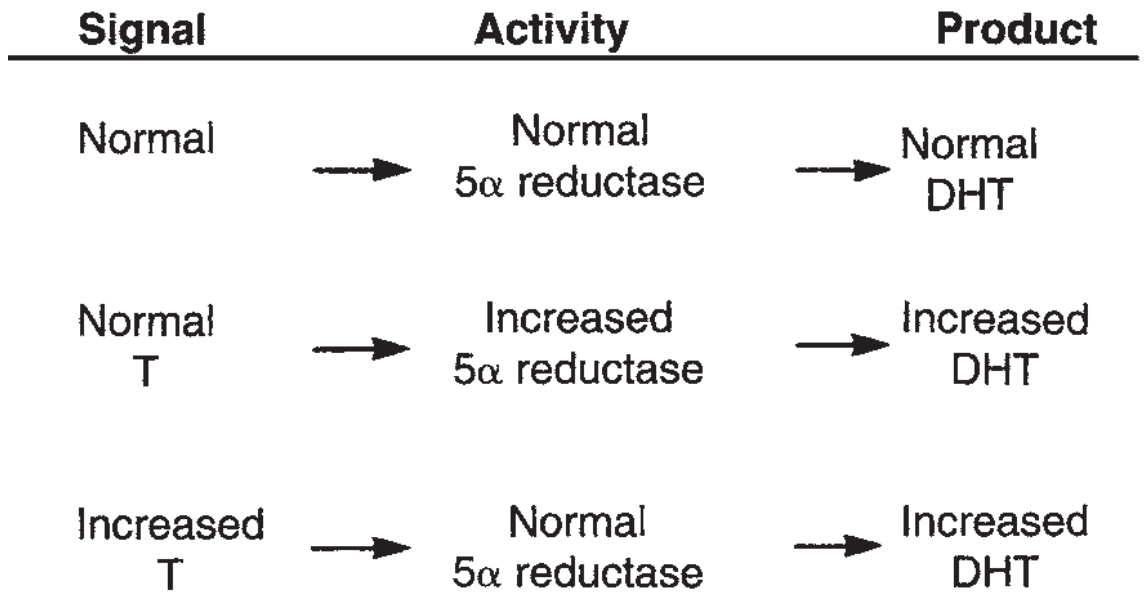

Figure 40.4 Influence of androgen substrate (signal; e.g., testosterone or androstenedione) and 5α-reductase activity (in pilosebaceous units) on local production of biologically active androgens. *T*, Testosterone; *DHT*, dihydrotestosterone. (From Lobo RA. Androgen excess. In: Mishell DR Jr, Davajan V, Lobo RA, eds. *Infertility, Contraception and Reproductive Endocrinology.* 3rd ed. Cambridge, MA: Blackwell Scientific; 1991.)

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PHYSIOLOGY OF ANDROGENS IN WOMEN

Table 40.4 Markers of Androgen Production

Source	Marker
Ovary	Testosterone
Adrenal gland	DHEAS
Periphery	3α-diol-G

From Lobo RA. Androgen excess. In: Mishell DR Jr, Davajan V, Lobo RA, eds. *Infertility, Contraception and Reproductive Endocrinology*. 3rd ed. Cambridge, MA: Blackwell Scientific; 1991.

DHEAS, Dehydroepiandrosterone sulfate; *3α-diol-G*, 5α-androstane-3α,17β-diol glucuronide.

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Table 40.5 Differential Diagnosis of Hirsutism and Virilization*

Source	Diagnosis
Nonspecific	Exogenous, iatrogenic
	Abnormal gonadal or sexual development
Pregnancy	Androgen excess in pregnancy, luteoma or hyperreactio luteinalis
Periphery	Idiopathic hirsutism
Ovary	Polycystic ovary syndrome†
	Functional or idiopathic hyperandrogenism‡
	Stromal hyperthecosis
	Ovarian tumors
Adrenal gland	Adrenal tumors
	Cushing syndrome
	Adult-onset congenital adrenal hyperplasia

*Idiopathic hirsutism and polycystic ovary syndrome do not present with virilization.
†The hyperandrogenism in PCOS can also be of adrenal origin, at least in part.
‡Functional hyperandrogenism may well be a type of PCOS, but without clearly defined polycystic ovaries on ultrasound, and can also have an adrenal source of hyperandrogenism.

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1. IDIOPATHIC HIRSUTISM (PERIPHERAL DISORDER OF ANDROGEN METABOLISM)

- signs of hirsutism + regular menstrual cycles + normal circulating levels of androgens
- *familial, constitutional, idiopathic hirsutism* (because neither ovarian nor adrenal androgen production is increased)
- there is an enhancement of androgen action in the PSU (i.e., an increased androgen sensitivity).
- women have increased levels of 3α-diol-G, indirectly indicating that the cause of hirsutism is largely the result of increased 5α-reductase activity
- idiopathic hirsutism is actually a disorder of the peripheral compartment and is possibly genetically determined, although it is also possible that early exposure to androgens can program increased 5α-RA.

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2. POLYCYSTIC OVARY SYNDROME

Table 41.1 Criteria for Diagnosis of Polycystic Ovary Syndrome

Study*	Criteria
National Institute of Child Health and Human Development 1990	Menstrual irregularity Hyperandrogenism (clinical or biochemical)
ESHRE-ASRM 2003 "Rotterdam criteria"	Menstrual irregularity Hyperandrogenism (clinical or biochemical) Polycystic ovaries on ultrasound (two of three required)
AEPCOS 2006	Hyperandrogenism (clinical or biochemical) and menstrual irregularity Polycystic ovaries on ultrasound (either or both of the latter two)
NIH Workshop 2012	Endorsement of Rotterdam criteria, acknowledging its limitations, and suggesting the name PCOS should be changed

*All required the exclusion of other underlying hormonal disorders or tumors.

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2. POLYCYSTIC OVARY SYNDROME

CAUSES OF ANDROGEN EXCESS OR HYPERANDROGENISM

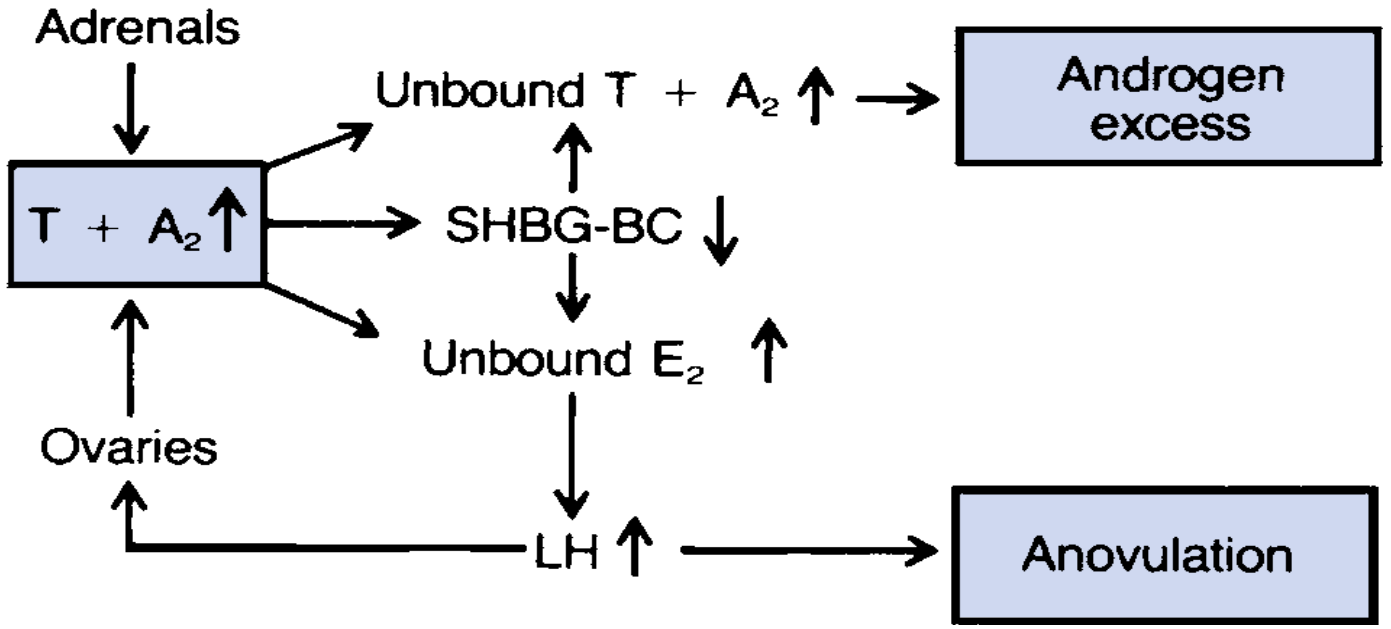

Figure 40.7 Scheme depicting the possible role of adrenal-derived androgen in initiating androgen excess and anovulation. *A_2*, Androstanediol; *E_2*, estradiol; *LH*, luteinizing hormone; *SHBG-BC*, sex hormone-binding globulin binding capacity; *T*, testosterone. (From Lobo RA, Goebelsmann U. Effect of androgen excess on inappropriate gonadotropin secretion as found in polycystic ovary syndrome. *Am J Obstet Gynecol.* 1982;142:394-401.)

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3. FUNCTIONAL OR IDIOPATHIC HYPERANDROGENISM

- diagnosed when androgens are elevated (either ovarian or adrenal) and menstrual cycles are regular and ovulatory.
- there is also no evidence on ultrasound for polycystic ovaries, making this an “idiopathic” state.
- Can be a variant of PCOS, in which women may be ovulatory.

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4. STROMAL HYPERTHECOSIS

- an uncommon benign ovarian disorder in which the ovaries are typically bilaterally enlarged to approximately 5 to 7 cm in diameter.
- Histologically, there are nests of luteinized theca cells within the stroma ; capsules of these ovaries are thick, similar to those found in PCOS but, unlike PCOS, subcapsular cysts are uncommon.
- the theca cells produce large amounts of testosterone,
- Like PCOS, this disorder has a gradual onset and is initially associated with anovulation or amenorrhea and hirsutism. However, unlike PCOS, with increasing age the ovaries secrete steadily increasing amounts of testosterone.
- there is also no evidence on ultrasound for polycystic ovaries, making this an “idiopathic” state.
- Can be a variant of PCOS, in which women may be ovulatory.

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4. STROMAL HYPERTHECOSIS

- the diagnosis of ovarian stromal hyperthecosis should be suspected for women with these signs and testosterone levels greater than 1.5 ng/mL.

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CAUSES OF ANDROGEN EXCESS OR HYPERANDROGENISM

5. ANDROGEN-PRODUCING TUMORS

- A. Ovarian neoplasms
- B. Adrenal tumors

** *Masculinizing ovarian or adrenal tumors are associated with rapidly progressive signs of hirsutism and virilization.*

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A. Ovarian neoplasms

- excess testosterone may be produced by benign and malignant cystadenomas, Brenner tumors, Krukenberg tumors, germ cell tumors such as Sertoli-Leydig cell tumors and hilus cell tumors, lipoid cell (adrenal rest) granulosa/theca cell tumors.
- Androgen-producing ovarian tumors usually produce rapidly progressive signs of virilization.
- **Sertoli-Leydig cell tumors** develop during the reproductive years (second to fourth decades) and, by the time they produce detectable signs of androgen excess, the tumor is almost always palpable during bimanual examination.
- **Hilus cell tumors** usually occur after menopause, are usually small and not palpable during bimanual examination; however, the history of rapid development of signs of virilization and the presence of markedly elevated levels of testosterone (> 2.5 times the upper limits of the normal range), with normal levels of DHEAS, usually facilitate the diagnosis.

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B. Adrenal Tumors

- Almost all the androgen-producing adrenal tumors are adenomas or carcinomas that generate large amounts of the C19 steroids normally produced by the adrenal gland—DHEAS, DHEA, and androstenedione.
- these tumors do not usually secrete testosterone directly (testosterone is produced by extraglandular conversion of DHEA and androstenedione).
- markedly elevated serum levels of DHEAS (>8 µg/mL).
- Women should undergo a CT scan or MRI of the adrenal glands to confirm the diagnosis.
- adrenal adenomas secrete large amounts of testosterone. Because adrenal adenomas also secrete DHEAS, an adrenal adenoma is highly likely when DHEAS levels are greater than 8 µg/ mL and testosterone levels are more than 1.5 ng/mL.

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5. ANDROGEN-PRODUCING TUMORS

- Serum testosterone levels higher than 2 ng/mL, with normal DHEAS levels, indicate the probable presence of an ovarian tumor.
  - the diagnosis can be confirmed by bimanual pelvic examination and ultrasonography, CT scan, or MRI.
- Women with a rapid progression of virilization and DHEAS levels greater than 8 µg/mL most likely have an androgen-producing adrenal adenoma; CT or MRI can confirm the diagnosis.
- A long history of gradually increasing hirsutism, even if accompanied by virilization, is not consistent with the diagnosis of adrenal or ovarian tumors.

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6. LATE-ONSET 21-HYDROXYLASE DEFICIENCY (LOHD)

- inherited disorder caused by an enzymatic defect (usually 21-hydroxylase [21- OHase] or, less often, 11β-hydroxylase), resulting in decreased cortisol biosynthesis.
- As a consequence, adrenocorticotropic hormone (ACTH) secretion increases and adrenal cortisol precursors produced proximal to the enzymatic block accumulate → these are converted mainly to 17-hydroxyprogesterone and androstenedione
- androstenedione in turn is converted to testosterone, which produces signs of androgen excess.

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CAUSES OF ANDROGEN EXCESS OR HYPERANDROGENISM

6. LATE-ONSET 21-HYDROXYLASE DEFICIENCY

- the classic severe form (complete block) usually becomes clinically apparent in fetal life by producing masculinization of the female external genitalia.
- the severe form of CAH is the most common cause of sexual ambiguity in the newborn.
- the mild block of 21-hydroxylase activity usually does not produce the physical signs associated with increased androgen production until after puberty → known as **late-onset 21-hydroxylase deficiency (LOHD)** or **late-onset congenital adrenal hyperplasia (LOCAH)**, is associated with the development of signs of hyperandrogenism in a woman in the *second or early third decade of life.*
- Both classic CAH and LOCAH are transmitted in an autosomal recessive manner at the *CYP21B* locus and are linked to the HLA-B locus.

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6. LATE-ONSET 21-HYDROXYLASE DEFICIENCY

- A spectrum of mutations results in the enzymatic defects and clinical presentations shown in Table

Table 40.6 Genotypic Characterization of the Forms of 21-Hydroxylase Deficiency

Form of 21-Hydroxylase Deficiency	Clinical Phenotype	Hormonal Phenotype (in Response to ACTH)	Genotype
Classic (CAH)	Prenatal virilization, fully symptomatic	Marked elevation of precursors (serum 17-hydroxyprogesterone and Δ-androstenedione)	21-OH-def^{severe} 21-OH-def^{severe}
Nonclassic (LOHD)	Symptomatic: later development of virilization; milder symptoms Asymptomatic: no virilization or other symptoms	Moderate elevation of precursors	21-OH-def^{severe} 21-OH-def^{mild} 21-OH-def^{mild} 21-OH-def^{mild}
Carrier	Asymptomatic	Precursor level greater than normal	21-OH-def^{severe} 21-OHase (normal) 21-OH-def^{mild} 21-OHase (normal) 21-OHase (normal) 21-OHase (normal)
Normal	Asymptomatic	Lowest levels—some overlap seen with carriers	

From New MI, White PC, Pang S, et al. The adrenal hyperplasias. In: Scriver CR, Beaudet AL, Sly S, Valle D, eds. *Metabolic Basis of Inherited Diseases*. 6th ed. New York: McGraw-Hill; 1989.

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6. LATE-ONSET 21-HYDROXYLASE DEFICIENCY

- LOCAH is also usually associated with menstrual irregularity → the increased levels of androgen lower SHBG levels, thus increasing the amount of biologically active circulating estradiol→ the increased estradiol stimulates tonic LH release, which increases ovarian androgen production and locally inhibits follicular growth and ovulation;
  - thus women with this disorder present with postpubertal onset of hirsutism and oligomenorrhea or amenorrhea, similar to women with PCOS.
- women with LOCAH, unlike those with PCOS, commonly have a history of prepubertal accelerated growth (at 6 to 8 years of age), with later decreased growth and a short ultimate height.
- A history of this growth pattern, a family history of postpubertal onset of hirsutism, and findings of mild virilization are indicators of the presence of CAH.

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6. LATE-ONSET 21-HYDROXYLASE DEFICIENCY

- To differentiate LOCAH from PCOS, measurement of basal (early morning) serum 17-hydroxyprogesterone levels should be performed:
  - If basal levels are greater than 8 ng/mL, the diagnosis of LOCAH is established.
  - If 17-hydroxyprogesterone is above normal (2.5 to 3.3 ng/mL) but less than 8 ng/mL, an ACTH stimulation test should be performed.
    - A baseline 17-hydroxyprogesterone level should be measured and 0.25 mg of synthetic ACTH infused as a single bolus.
    - One hour later, another serum sample of 17-hydroxyprogesterone should be measured. If the level increases more than 10 ng/mL, the diagnosis of LOCAH is established
- Corticosteroid treatment is normally reserved for patients wishing to conceive to restore ovulatory function

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6. LATE-ONSET 21-HYDROXYLASE DEFICIENCY

- It is important to measure 11-desoxycortisol during the ACTH stimulation when the diagnosis is being evaluated, because of the possibility of 11-hydroxylase deficiency. I
- this disorder is much more rare, but it also has an incomplete, adult form and may also be associated with hypertension.
- Women with this incomplete form also have increases in 17-hydroxyprogesterone and thus require the measurement of 11-desoxycortisol to differentiate it from 21-hydroxylase deficiency.

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Note:

- PCOS, LOHD, and idiopathic hirsutism or those women diagnosed with functional hyperandrogenism may be associated with a similar history and findings at physical examination.
- Women with LOHD commonly have a family history of androgen excess and often belong to an ethnic group with a higher gene frequency for an abnormality.
- the diagnosis of LOHD is established by measurement of 17-hydroxyprogesterone, either by testing of an early morning serum sample or following ACTH stimulation.

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7. CUSHING SYNDROME

- Excessive adrenal production of glucocorticoids caused by increased ACTH secretion (Cushing disease) or adrenal tumors.
- hirsutism and menstrual irregularity, in addition to the classic findings of central obesity, dorsal neck fat pads, abdominal striae, and muscle wasting and weakness.
- the latter catabolic effect of glucocorticoid excess differs from the anabolic effects of testosterone excess, but some women with PCOS may have other clinical findings similar to those found with Cushing syndrome.
- Women with Cushing syndrome are more likely to present with other symptoms and signs of glucocorticoid excess, rather than because of hirsutism; but this has been found to occur in fewer than1% of cases.

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CAUSES OF ANDROGEN EXCESS OR HYPERANDROGENISM

7. CUSHING SYNDROME

- Cushing syndrome can be easily excluded by performing an overnight dexamethasone suppression test (DST):
  - 1 mg of dexamethasone is ingested at 11 pm, and the plasma cortisol level is measured the following morning, at 8 am.
  - If the cortisol level is <5 µg/100 mL, Cushing syndrome is ruled out.
  - If the cortisol level > 5 µg/100 mL → It is necessary to perform a complete dexamethasone suppression test (Liddle test) or measure the urinary free cortisol and plasma ACTH levels to determine whether Cushing syndrome exists.

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CAUSES OF ANDROGEN EXCESS OR HYPERANDROGENISM

7. CUSHING SYNDROME

- many endocrinologists prefer 24-hour urinary free cortisol level or salivary cortisol.
  - A creatinine level is also measured to gauge completeness of urine collection.
  - Values above 100 µg/24 hours in urine are abnormal
  - values greater than 240 µg are almost diagnostic of Cushing syndrome.
- Late night salivary cortisol is now considered to be the most accurate method. Samples are usually obtained on two separate nights:
  - values > 0.4 µg/dL are diagnostic for Cushing syndrome
- Cushing syndrome may result from a pituitary tumor producing ACTH (Cushing disease), an ectopic tumor in the body, adrenal neoplasms, or hyperplasia.

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GENERAL LAB WORK-UPS FOR HYPERANDROG-ENISM

- the laboratory workup should include:
  - testosterone (unbound testosterone or the free androgen index [testosterone/SHBG is optional])
  - DHEAS
  - 17 hydroxyprogesterone when LOCAH is suspected (younger individuals, family history of androgen excess, and in high prevalent ethnic groups).

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TREATMENT

1. Ovarian and Adrenal Tumors

- Best identified by high-grade imaging techniques.
- Almost all Sertoli-Leydig cell tumors are unilateral. If the woman has not completed her family and these tumors are well differentiated and confined to one ovary, the tumors may be treated by unilateral salpingooophorectomy.
- Because most hilus cell tumors occur after menopause, they are best treated by bilateral salpingooophorectomy and total abdominal hysterectomy.

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TREATMENT

1. Ovarian and Adrenal Tumors

- Adrenal adenomas and carcinomas should also be treated by operative removal.
- Adrenal carcinomas frequently have metastasized to the liver by the time the androgenic signs have developed.
- Despite chemotherapy, the prognosis is poor after metastases have occurred.

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TREATMENT

2. Stromal hyperthecosis

- best treated by bilateral salpingooophorectomy.
- After removal of the ovaries of women with stromal hyperthecosis or any of the androgen-producing tumors, the acne and oiliness of the skin disappear, breast size increases, and clitoral size decreases.
- the excess central hair becomes finer and grows less rapidly but does not disappear.
- Electrolysis or laser treatment can remove the body hair more effectively

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TREATMENT

3. Late-Onset 21-Hydroxylase Deficiency (Congenital Adrenal Hyperplasia/LOHD/LOCAH)

- treatment of women with LOCAH depends on their primary complaint:
  - androgen excess and menstrual irregularity can be treated as in women with PCOS, usually with an oral contraceptives.
  - if women wish to conceive, it is preferable to use glucocorticoids such as hydrocortisone (15 to 20 mg), prednisone (5 to 7.5 mg), or dexamethasone (0.5 to 0.75 mg) in divided doses. → Doses as low as 2.5 mg of prednisone or 0.25 mg dexamethasone may be used initially.
  - the aim of treatment is to suppress androstenedione and bring 17-hydroxyprogesterone and progesterone levels into the normal range. Ovulation usually resumes rapidly

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TREATMENT

4. PCOS

- a successful strategy usually requires an antiandrogen added to suppression therapy (usually OCP)
- Among the various preparations, it would seem logical to use a less androgenic progestogen (norgestimate, desogestrel, drospirenone) than more potent ones (levonorgestrel).
- In women with more significant complaints and findings, an antiandrogen can be used initially.
- It is important to use antiandrogens in conjunction with an OCPs because of the concerns of exposure during pregnancy.
- Oral contraceptives suppress ovarian androgens by inhibiting LH stimulation of the ovary.
- Oral contraceptives decrease adrenal androgens (DHEAS) by about 30% and inhibit 5α-reductase activity.
- ethinyl estradiol in contraceptives increases SHBG, which results in lower free or unbound testosterone.

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TREATMENT

4. PCOS

Antiandrogens

- Includes androgen receptor blockers **spironolactone** and **flutamide** and a 5α-2 inhibitor, **finasteride.**
- Cyproterone acetate (2 mg) is an anti-androgenic progestin (most frequently used in combination with ethinyl estradiol as an OC)
- Drospirenone in the doses used in contraceptives (3 mg) does not have appreciable antiandrogenic activity.
- Spironolactone also decreases ovarian testosterone production and inhibits 5α-RA:
  - a dose of 200 mg/ day of spironolactone x 3 months is effective than 100 mg/day
  - After 1 year of treatment, a 15% to 25% reduction in hair shaft diameter and linear growth rate at all body sites.

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TREATMENT

3. PCOS

Antiandrogens

- Flutamide (250 to 750 mg/day); the major concern is hepatic toxicity which may lead to death.
  - Most guidelines have advised against the use of flutamide for this reason; and if it is used it should be used with caution at lower doses and with close monitoring of hepatic function. As with other antiandrogens, contraception should be used.
- Finasteride, a 5α-reductase inhibitor (5 mg/day)
  - Finasteride is used currently as a second-line treatment when there are side effects or problems with using spironolactone.

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TREATMENT

Other Agents for Treatment

- **GnRH agonist** with estrogen or an OC add-back has been shown to be successful; expensive and cannot be used for long-term therapy.
- **Ketoconazole** blocks adrenal and gonadal steroidogenesis by inhibiting cytochrome P450–dependent enzyme pathways
  - 200 mg twice daily, to treat hyperandrogenism associated with PCOS and idiopathic hirsutism.
  - this potent drug effectively decreases hair growth and acne, but major side effects and complications (including hepatitis) occur in most women
- **Glucocorticoids** suppress the adrenal gland in women who have adrenal androgen excess, and low doses have been used with some degree of success
  - Because of its potential for serious side effects, glucocorticoids are not recommended for treating androgen excess but may be considered as an adjunct to ovulation induction in some women.

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TREATMENT

Other Agents for Treatment

- **Insulin sensitizers** have been proposed as agents to treat androgen excess and have been used in women with PCOS.
  - not recommended as a primary therapy for manifestations of androgen excess
- **Eflornithine cream 13.9%** is a topical treatment that has been approved by the U.S. Food and Drug Administration (FDA) for facial hirsutism.
  - Eflornithine is an inhibitor of ornithine decarboxylase, which is an enzyme necessary for the growth and development of the hair follicle.
  - It was originally developed for the treatment of trypanosomal sleeping sickness.
  - It is approved only for facial hirsutism and its mechanism is such that it affects all hair follicles and is not specific for hirsutism;
  - application twice a day results in a modest improvement in about 8 weeks.

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Follow-up for Treatment of Hirsutism

- Because of the length of the hair growth cycle, responses to treatment should not be expected to occur within the first 3 months of therapy
  - usually takes about 6 months to see a response.
- Objective methods of assessing changes of hair growth, such as photographs, are useful.
- With the use of various therapies, a successful response for hirsutism should occur in approximately 70% of women within 1 year of therapy.
- Remaining excess hair can be removed by electrolysis or laser techniques.
- Treatment should be continued for 3 years and then stopped to determine whether hirsutism recurs. If so, therapy can be reinitiated.

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Hair Removal Techniques

- cosmetic measures can be used as a primary treatment for mild isolated hirsutism or should be initiated after adequate suppressive therapy to remove unwanted hair once the growth rate has been inhibited by therapy.
- definitive therapies include the use of electrolysis and lasers
- **Electrolysis** uses electrical energy through a wire electrode. Destruction of hair follicles results in its permanent removal.
- **Photoepilation** uses lasers that apply heat to pigmented hair follicles.
  - There are four types of lasers: Nd:Yag, diode, alexandrite, and ruby,.

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Acne

- Among hyperandrogenic disorders, acne vulgaris is the disorder that is most successfully treated, with response rates of close to 90%.
- androgens stimulate sebum production, and high doses of estrogen can inhibit it.
- Among women who present with acne, 52% can be found to have androgen excess, with increases in unbound testosterone being the most frequently encountered
  - women who present with significant acne, particularly if they have not responded to routine dermatologic measures, an evaluation of androgen excess is warranted.
  - An enhancement of 5α-reductase, mostly type 1, is a large part of the androgen abnormalities in acne
- Treatment is usually with combination oral contraceptives
  - OCPs containing less androgenic progestogens are preferred
  - If oral contraceptives alone are not completely successful, as with hirsutism, the addition of antiandrogens are beneficial

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Alopecia

- Previously called androgenic alopecia, the preferred term currently is **female pattern hair loss (FPHL).**
- this may or may not be associated with androgen excess.
- With androgen excess, exaggerated 5α-reductase activity has been implicated in women with alopecia
- Hair loss is usually on the frontal scalp and vertex, with relative sparing of the occipital scalp.
- Antiandrogen therapy is the mainstay of treatment.
  - In women, spironolactone and FLtamide (to be used with caution) are effective
  - finasteride, which is used widely in men, is not effective in women.
  - Minoxidil is also used to stimulate hair growth

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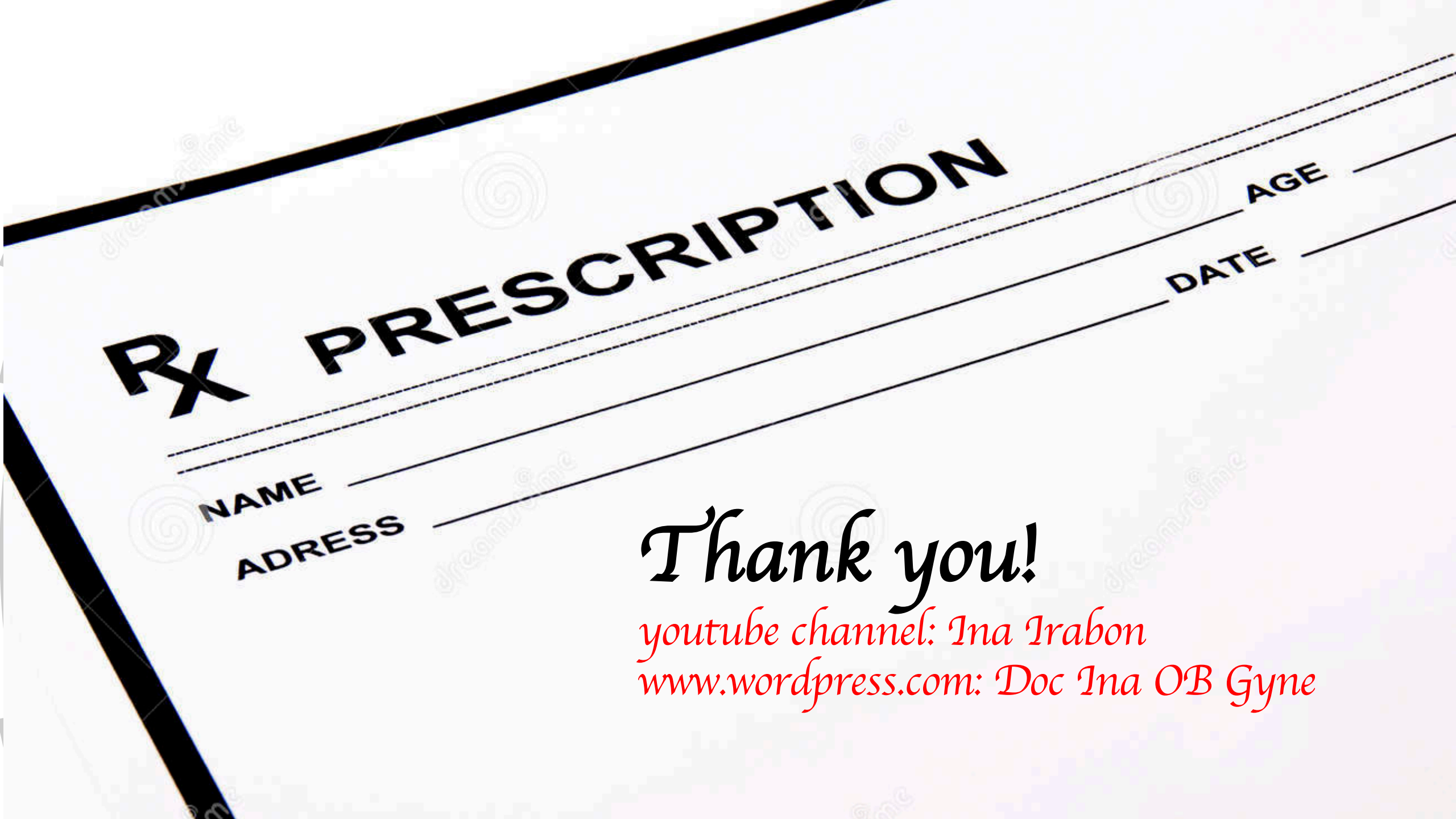
Summary

- Review of Pilosebaceous unit
- Physiology of androgens in women
- Causes of hyperandrogenism
- Treatment



Thank you!

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