21 - 406 Hirsutism

406 Hirsutism

as appropriate. Neuromuscular and psychosomatic etiologies should also be considered. Some women experience discomfort at the time of ovulation (mit telschmerz or ovulation pain). The pain can be quite intense but is generally of short duration. The mechanism is thought to involve rapid expansion of the dominant follicle, although it also may be caused by peritoneal irritation by follicular fluid released at the time of ovulation. Dysmenorrhea typically refers to the crampy lower abdominal mid line discomfort that begins with the onset of menstrual bleeding and gradually decreases over 12–72 h. It may be associated with nausea, diarrhea, fatigue, and headache and occurs in 60–93% of adolescents, beginning with the establishment of regular ovulatory cycles. Its preva lence decreases after pregnancy and can be treated effectively with hormonal contraceptives. Primary dysmenorrhea results, in a major ity of cases, from hormone-dependent prostaglandin (PG) pathway mechanisms that cause intense uterine contractions, decreased blood flow, and increased peripheral nerve hypersensitivity, resulting in pain. However, variability in response to cyclooxygenase inhibitors suggests that PG-independent pathways, such as platelet activating factor, may also mediate inflammation. Secondary dysmenorrhea refers to pain caused by underlying pelvic pathology. Endometriosis results from the presence of endometrial glands and stroma outside the uterus. These deposits of ectopic endometrium respond to hormonal stimulation and may be associated with dysmen orrhea, painful intercourse, and painful bowel movements. On pelvic exam, adnexal tenderness may be present or tender nodules may be palpated along the uterosacral ligaments. Pain associated with endo metriosis can be cyclic or continuous, and the stage/severity of endo metriosis, as determined by laparoscopy, does not always correlate with the extent of pain. Transvaginal pelvic ultrasound is part of the initial workup and may detect an endometrioma within the ovary. Additional sonographic techniques can be used to identify deep endometriosis including nonmobile ovaries and rectovaginal or bladder nodules. The CA-125 level may be increased, but it has low negative predictive value. Pelvic MRI has higher sensitivity and specificity for diagnosis of endometriosis. Diagnostic laparoscopy is performed when patients do not respond adequately to empiric treatment and is considered the gold standard for diagnosis. If endometriosis is detected, the severity can be staged and the endometriotic lesions ablated or excised. Large fibroids can cause chronic pelvic pain or pressure, and submu cosal fibroids may be associated with dysmenorrhea. Other secondary causes of dysmenorrhea include adenomyosis, a condition caused by the presence of ectopic endometrial glands and stroma within the myo metrium. Chronic PID may be associated with ongoing pelvic pain and is associated with tuberculosis or actinomycosis. Pelvic congestion syn drome is associated with pelvic varicosities with low blood flow, result ing in pelvic venous congestion. However, this is no clear evidence to indicate that this finding is associated with chronic pelvic pain. TREATMENT Chronic Pelvic Pain DYSMENORRHEA Local application of heat, exercise, sexual activity, a vegetarian diet, use of vitamins D, B1, B6, and E and fish oil, acupuncture, and yoga have all been suggested to be of

benefit, but studies are not adequate to provide recommendations. However, NSAIDs are very effective and provide >80% sustained response rates. Ibuprofen, naproxen, ketoprofen, mefenamic acid, and nimesulide are all superior to placebo. For best response, treatment should be initiated prior to the onset of menses and continued for at least 2–3 days. Combined or progestin-only hormonal contraceptives taken cyclically or con tinuously effectively reduce symptoms of dysmenorrhea. ENDOMETRIOSIS Combined hormonal contraceptives or continuous progestin (either orally, implants, or a levonorgestrel IUD) is used for the treatment of endometriosis. Evidence of an endometrioma on ultrasound

imaging can be medically managed and does not require surgi cal removal unless it increases in size or there is persistent pain. Patients who do not respond to medical management and lapa roscopic resection of endometriotic lesions can be offered GnRH agonist suppression with add-back therapy or aromatase inhibitors. FIBROIDS Chronic pain and dysmenorrhea associated with fibroids can be managed medically or surgically depending on the number and location of fibroids and associated symptoms. The U.S. Food and Drug Administration (FDA) approved the first two oral treat ments for uterine fibroids (elagolix with estradiol/norethindrone acetate and relugolix with estradiol/norethindrone acetate), and the selective progesterone receptor modulator ulipristal acetate was withdrawn in Europe and Canada. Medical management includes oral hormonal contraceptives, tranexamic acid, NSAIDs, proges tins, IUDs, and GnRH agonists and antagonists. Surgical man agement includes myomectomy, endometrial ablation/myolysis, radiofrequency volumetric thermal ablation, laparoscopic ablation, or hysterectomy. Chronic pain and dysmenorrhea associated with adenomyosis can be managed with combined hormonal treat ment, levonorgestrel IUD, or hysterectomy after child-bearing is complete.

Hirsutism CHAPTER 406 ■ ■FURTHER READING Bartels CB et al: An evidence-based approach to the medical man agement of fibroids: A systematic review. Clin Obstet Gynecol 59:30, 2016. Bloomfield H et al: Screening pelvic examinations in asymptomatic average risk adult women. WA-ESP Project #09-009; 2013. Bouilly J et al: Identification of multiple gene mutations accounts for the new genetic architecture of ovarian insufficiency. J Clin Endocrinol Metab 101:4541, 2016. Brunham RC et al: Pelvic inflammatory disease. N Engl J Med 372:2039, 2015. Fourman LR, Fazeli PK: Neuroendocrine causes of amenorrhea—An update. J Clin Endocrinol Metab 100:812, 2015. Ju H et al: The prevalence and risk factors of dysmenorrhea. Epidem Rev 36:104, 2014. Lee IT, Barnhart KT: What is an ectopic pregnancy? JAMA 329:434, 2023. Oladosu FA et al: Nonsteroidal anti-inflammatory drug resistance in dysmenorrhea: Epidemiology, causes, and treatment. Am J Obstet Gynecol 218:390, 2018. Taylor HS et al: Endometriosis is a chronic systemic disease: Clinical challenges and novel innovations. Lancet 397:839, 2021. Teede HJ et al: International PCOS Network. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Fertil Steril 120:767, 2023. David A. Ehrmann

Hirsutism ■ ■DEFINING HIRSUTISM Body hair can be categorized as either vellus (fine, soft, and not pig mented) or terminal (long, coarse, and pigmented). Approximately 10% of reproductive-age women have hirsutism, defined by the presence of excessive terminal hair growth. Hirsutism is most often idiopathic or the consequence of androgen excess associated with polycystic ovary

TABLE 406-1 Causes of Hirsutism Gonadal hyperandrogenism Ovarian hyperandrogenism Polycystic ovary syndrome/functional ovarian hyperandrogenism Ovarian steroidogenic blocks Syndromes of extreme insulin resistance Ovarian neoplasms Hyperthecosis Adrenal hyperandrogenism Premature adrenarche Functional adrenal hyperandrogenism Congenital adrenal hyperplasia (nonclassic and classic) Abnormal cortisol action/metabolism Adrenal neoplasms Other endocrine disorders Cushing's syndrome Hyperprolactinemia Acromegaly Peripheral androgen overproduction Obesity Idiopathic Pregnancy-related hyperandrogenism Hyperreactio luteinalis Thecoma of pregnancy Drugs Androgens Oral contraceptives containing androgenic progestins Minoxidil Phenytoin Diazoxide Cyclosporine Valproic acid Ovotesticular disorders of sex development PART 12 Endocrinology and Metabolism syndrome (PCOS). Less frequently, it results from adrenal androgen overproduction as occurs in nonclassic congenital adrenal hyperplasia (CAH) (Table 406-1). Virilization refers to a condition that may the result from benign hyperplasia of ovarian theca and stroma cells (e.g., hyperthecosis); it may also be a harbinger of a serious underlying condition, such as an ovarian or adrenal neoplasm. In women with virilization, androgen levels are sufficiently high to cause deepening of the voice, breast atro phy, increased muscle bulk, clitoromegaly, and increased libido. Cuta neous manifestations commonly associated with hirsutism include acne and hair thinning or pattern hair loss (androgenic alopecia). ■ ■HAIR FOLLICLE GROWTH AND DIFFERENTIATION The number of hair follicles remains unchanged over the life span, but follicle size and the type of hair can change in response to numerous factors, particularly androgens. Androgens are necessary for terminal hair and sebaceous gland development and mediate differentiation of pilosebaceous units (PSUs) into a terminal hair follicle and/or a sebaceous gland. In the former case, androgens transform the vellus hair into a terminal hair; in the latter case, the sebaceous component proliferates and the hair remains vellus. There are three phases in the cycle of hair growth: (1) anagen (growth phase), (2) catagen (involution phase), and (3) telogen (rest phase). Depending on the body site, hormonal regulation may play an important role in the hair growth cycle. Hair growth on the face, chest, upper abdomen, and back typically requires elevated androgen concen trations. However, there is only a modest correlation between androgen levels and the quantity of hair growth. This is due to the fact that hair growth from the follicle also depends on local growth factors, and the variability in end-organ (PSU) sensitivity to androgens. Genetic factors

and ethnic background also influence hair growth. Androgen excess in women may result in hair thinning or loss because androgens cause scalp hairs to spend less time in the anagen phase. In general, dark-haired individuals tend to be more hirsute than blond or fair individuals. Asians and Native Americans have relatively sparse hair in regions sensitive to high androgen levels, whereas people of Mediterranean descent are more hirsute. ■ ■CLINICAL ASSESSMENT Historic elements relevant to the assessment of hirsutism include the age at onset and rate of progression of hair growth and associated symptoms or signs (e.g., menstrual irregularity and acne). Depend ing on the cause, excess hair growth typically is first noted during the second and third decades of life. The growth is usually slow but progressive. Sudden development and rapid progression of hirsutism suggest the possibility of an androgen-secreting neoplasm, in which case virilization may also be present. The age at onset of menstrual cycles (menarche) and the pattern of the menstrual cycle should be ascertained. Menses may be irregular in the first 2 years after menarche; oligomenorrhea (<8 cycles per calen dar year) thereafter is more likely to result from ovarian than adrenal androgen excess. Associated symptoms such as galactorrhea should prompt evaluation for hyperprolactinemia (Chap. 392) or possibly hypothyroidism (Chap. 394). Hypertension, striae, easy

bruising, and centripetal weight gain suggest hypercortisolism (Cushing’s syndrome; Chap. 398). Rarely, patients with acromegaly present with hirsutism. Medications such as phenytoin, minoxidil, and cyclosporine may be associated with androgen-independent excess hair growth (i.e., hyper trichosis). A family history of infertility and/or hirsutism may indicate inherited disorders such as nonclassic CAH (Chap. 398). Physical examination should include measurement of height and weight and calculation of body mass index (BMI). A BMI >25 kg/m2 is indicative of excess weight for height, and values >30 kg/m2 are often seen in association with hirsutism, probably the result of increased conversion of androgen precursors to testosterone. Notation should be made of blood pressure, as adrenal causes may be associated with hypertension. Cutaneous signs sometimes associated with androgen excess and insulin resistance include acanthosis nigricans and skin tags. An objective clinical assessment of hair distribution and quantity is central to the evaluation in any woman presenting with concerns about excessive hair growth. This assessment permits the distinction between hirsutism and hypertrichosis and provides a baseline reference point to gauge the response to treatment. A simple and commonly used method to grade hair growth is the modified scale of Ferriman and Gallwey (Fig. 406-1), in which each of nine androgen-sensitive sites is graded from 0 (no hair growth) to 4 (hair growth typically seen in adult men). Although it is normal for most women to have some hair growth in androgen-sensitive sites, ~95% of non-Hispanic white and African American women have a score <8 on this scale. Scores >8 suggest excess androgen-mediated hair growth, a finding that should be assessed further by means of hormonal evaluation (see below). Asian and Native Ameri can women are less likely to manifest hirsutism, and the only cutaneous evidence of androgen excess may be pustular acne and thinning scalp hair. ■ ■HORMONAL EVALUATION Androgens are secreted by the ovaries and adrenal glands in response to their respective tropic hormones: luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH). Testosterone is the principal circulating steroid involved in the etiology of hirsutism; other steroids that may contribute to the development of hirsutism include andro stenedione and dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS). The ovaries and adrenal glands normally contribute about equally to testosterone production. Approximately half of the total tes tosterone originates from direct glandular secretion, and the remainder is derived from the peripheral conversion of androstenedione and DHEA (Chap. 393). Testosterone is the most important circulating androgen, but it is a precursor hormone in mediating hirsutism. Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase, which is

Upper lip

Chin

Chest

Abdomen

Pelvis

Upper arms

Thighs

Upper back

Lower back

FIGURE 406-1 Hirsutism scoring scale of Ferriman and Gallwey. The nine body areas that have androgen-sensitive areas are graded from 0 (no terminal hair) to 4 (frankly virile) to obtain a total score. A normal hirsutism score is <8. (Modified with permission from LJ DeGroot, JL Jameson: Endocrinology, 5th ed. Philadelphia, PA: Saunders; 2006.) located in the PSU. DHT is more potent than testosterone as it has a higher affinity for, and slower dissociation from, the androgen recep tor. The local production of DHT allows it to serve as the primary mediator of androgen action at the level of the PSU. There are two isoenzymes of 5α-reductase: type 2 is found in the prostate gland and in hair follicles, and type 1 is found primarily in sebaceous glands.

Hirsutism CHAPTER 406

One approach to the evaluation and treatment of hirsutism is depicted in Fig. 406-2. In addition to measuring blood levels of testosterone and DHEAS, it is often important to measure the level of free (or unbound) testosterone, i.e., the fraction of testosterone that is not bound to its carrier protein, sex hormone–binding globulin (SHBG). Unbound testosterone is biologically available for conversion to DHT

Evaluation and Treatment of Hirsutism Abnormal hirsutism score or localized terminal hair growth plus clinical evidence of a hyperandrogenic disorder Localized terminal hair growth (e.g., chin) Trial of dermatologic therapy PART 12 Endocrinology and Metabolism Course stable or improving Hair growth progresses Total testosterone blood level by specialty assay Normal variant Testosterone normal Hirsutism moderate-severe and/or other clinical evidence of hyperandrogenic endocrine disorder Hirsutism mild and isolated Hyperandrogenemia Trial of dermatologic or oral contraceptive therapy Free testosterone blood level (calculated from total testosterone and SHBG or by LC/TMS) Hair growth progresses Course stable or improving Free testosterone normal Idiopathic hirsutism Re-evaluate if hirsutism progresses FIGURE 406-2 Algorithm for the evaluation and treatment of hirsutism. LC/TMS, liquid chromatography/tandem mass spectrometry; SHBG, sex hormone–binding globulin. (Reproduced with permission from KA Martin et al: Evaluation and treatment of hirsutism in premenopausal women: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 103:1233, 2018.) and binding to androgen receptors. Both hyperinsulinemia and andro gen excess decrease hepatic production of SHBG, resulting in levels of total testosterone within the high-normal range, whereas the unbound hormone is elevated more substantially. Although there is a decline in ovarian testosterone production after menopause, ovarian estrogen production decreases to an even greater extent, and the concentration of SHBG is reduced. Consequently, there is an increase in the relative proportion of unbound testosterone, and it may exacerbate hirsutism after menopause. A baseline plasma total testosterone level >12 nmol/L (>3.5 ng/mL) usually indicates an androgen-producing tumor, whereas a level

> 7 nmol/L (>2 ng/mL) is suggestive of tumor but may also be observed in women with hyperthecosis. A basal DHEAS level >18.5 µmol/L (>7000 µg/L) suggests an adrenal tumor. Although DHEAS has been proposed as a “marker” of predominant adrenal androgen excess, it is not unusual to find modest

> elevations in DHEAS among women with PCOS. Computed tomography (CT) or magnetic resonance imaging (MRI) should be used to localize an adrenal mass, and transvaginal ultrasound usually suffices to identify an ovarian mass if clinical evalu ation and hormonal levels suggest these possibilities. PCOS is the most common cause of ovarian androgen excess (Chap. 404). An increased ratio of LH to follicle-stimulating hor mone (FSH) is characteristic in carefully studied patients with PCOS. However, because of the pulsatile nature of gonadotropin secretion, a random measurement of LH and FSH may be misleading and is not

Medication-related hair growth Discontinue if possible Testosterone elevated Major hyperandrogenic endocrine disorders to consider: • Polycystic ovary syndrome • Nonclassic congenital adrenal hyperplasia • Cushing's syndrome • Virilizing tumor • Hyperprolactinemia Free testosterone elevated recommended. Transvaginal ultrasound classically shows enlarged ovaries, increased stroma, and multiple "cysts" in women with PCOS. These so-called cysts are, in fact, preantral and early antral follicles that result from abnormal follicular maturation. "Cystic" ovaries also may be found in women with hypothalamic amenorrhea (Chap. 404) and even among women without clinical or laboratory features of PCOS. Thus, ultrasonography is often not needed to diagnose PCOS given its relatively low specificity and its high degree of operator dependence. Because adrenal androgens are readily suppressed by low doses of glucocorticoids, the dexamethasone androgen-suppression test may broadly distinguish ovarian from adrenal androgen overproduction. A blood sample is obtained before and after the administration of dexamethasone (0.5 mg orally every 6 h for 4 days). An adrenal source is suggested by suppression of unbound testosterone into the normal range; incomplete suppression suggests ovarian androgen excess. An overnight 1-mg dexamethasone suppression test, with measurement of 8:00 a.m. serum cortisol, is useful when there is clinical suspicion of Cushing's syndrome (Chap. 398). Nonclassic CAH is most commonly due to 21-hydroxylase defi ciency but also can be caused by autosomal recessive defects in other steroidogenic enzymes necessary for adrenal corticosteroid synthesis (Chap. 398). Because of the enzyme defect, the adrenal gland cannot secrete glucocorticoids (especially cortisol) efficiently. This results in diminished negative feedback inhibition of ACTH, leading to

compensatory adrenal hyperplasia and the accumulation of steroid precursors that subsequently are converted to androgen. Deficiency of 21-hydroxylase can be reliably excluded by determining a morning 17-hydroxyprogesterone level <6 nmol/L (<2 μg/L) (drawn in the follicular phase). Alternatively, 21-hydroxylase deficiency can be diag nosed by measurement of 17-hydroxyprogesterone 1 h after the admin istration of 250 μg of synthetic ACTH (cosyntropin) intravenously. TREATMENT Hirsutism Treatment of hirsutism may be accomplished pharmacologically or by mechanical means of hair removal. Nonpharmacologic treat ments should be considered in all patients either as the only treat ment or as an adjunct to drug therapy. Nonpharmacologic treatments include (1) bleaching, (2) removal of the hair from the skin surface by shaving or with chemical treat ments, and (3) depilatory (removal of the hair including the root) such as plucking, waxing, electrolysis, laser, and intense pulsed light (IPL). Despite perceptions to the contrary, shaving does not increase the rate or density of hair growth. Chemical depilatory treatments may be useful for mild hirsutism that affects only limited skin areas, although they can cause skin irritation. Wax treatment removes hair temporarily but is uncomfortable. Electrolysis is

effec tive for more permanent hair removal, particularly in the hands of a skilled electrologist. Laser and IPL are used to treat large areas of pigmented, terminal hair. Light of specific wavelength, duration, and energy is absorbed by melanin in the hair shaft and follicle lead ing to photothermolysis. Properly delivered, this treatment delays hair regrowth and causes permanent hair removal in many patients. Pharmacologic therapy is directed at interrupting one or more of the steps in the pathway of androgen synthesis and action: (1) suppression of adrenal and/or ovarian androgen production, (2) enhancement of androgen-binding to plasma-binding proteins, particularly SHBG, (3) impairment of the peripheral conversion of androgen precursors to active androgen, and (4) inhibition of androgen action at the target tissue level. Attenuation of hair growth is typically not evident until 4–6 months after initiation of medical treatment and, in most cases, leads to only a modest reduction in hair growth. Combination estrogen-progestin therapy in the form of an oral contraceptive is usually the first-line endocrine treatment for hirsut ism and acne, after dermatologic management. The estrogenic com ponent of most oral contraceptives currently in use is either ethinyl estradiol or mestranol. The suppression of LH leads to reduced production of ovarian androgens. The reduced androgen levels also result in a dose-related increase in SHBG, thus lowering the fraction of unbound plasma testosterone. Estrogens also have a direct, dosedependent suppressive effect on sebaceous cell function. The choice of a specific oral contraceptive should be predi cated on the progestational component, as progestins vary in their suppressive effect on SHBG levels and in their androgenic potential. Ethynodiol diacetate has relatively low androgenic poten tial, whereas progestins such as norgestrel and levonorgestrel are particularly androgenic, as judged from their attenuation of the estrogen-induced increase in SHBG. Norgestimate exemplifies the newer generation of progestins that are virtually “nonandro genic.” Drospirenone, an analogue of spironolactone that has both antimineralocorticoid and antiandrogenic activities, is often used as a progestational agent in combination with ethinyl estradiol, although concern remains about is prothrombotic effects. Oral contraceptives are contraindicated in women with a his tory of thromboembolic disease and women with increased risk of breast or other estrogen-dependent cancers (Chap. 407). There is a relative contraindication to the use of oral contraceptives in smok ers and those with hypertension or a history of migraine headaches. Improvements in hirsutism are typically in the range of 20%, but there may be an arrest of further progression of hair growth. In

most trials, estrogen-progestin therapy alone improves the extent of acne by an average of 50%. The effect on hair growth may not be evident for 6 months, and the maximum effect may require 9–12 months owing to the length of the hair growth cycle

Because oral contraceptives are efficacious and have fewer side effects, they are recommended over glucocorticoids as first-line treatment of hirsutism in CAH. If the response to oral contracep tives is inadequate, glucocorticoids may be used. The lowest effec tive dose of glucocorticoid should be used (e.g., dexamethasone [0.2–0.5 mg] or prednisone [5–10 mg]) taken at bedtime to achieve maximal suppression by inhibiting the nocturnal surge of ACTH. Hirsutism CHAPTER 406 Cyproterone acetate is the prototypic antiandrogen. It acts mainly by competitive inhibition of the binding of testosterone and DHT to the androgen receptor. In addition, it may enhance the metabolic clearance of testosterone by inducing hepatic enzymes. Although not available for use in the United States, cyproterone acetate is widely used in Canada, Mexico, and Europe. Cyproterone (50–100 mg) is given on days 1–15, and ethinyl estradiol (50 μg) is given on days 5–26 of the menstrual cycle. Side effects include irregular uterine bleeding, nausea, headache, fatigue, weight gain, and decreased libido. Spironolactone, which usually is used as a mineralocorticoid antagonist,

is also a weak antiandrogen. It is almost as effective as cyproterone acetate when used at high enough doses (100–200 mg daily). Patients should be monitored intermittently for hyperkale mia or hypotension, though these side effects are uncommon. Preg nancy should be avoided because of the risk of feminization of a male fetus. Spironolactone can also cause menstrual irregularity. It often is used in combination with an oral contraceptive, which sup presses ovarian androgen production and helps prevent pregnancy. Flutamide is a potent nonsteroidal antiandrogen that is effective in treating hirsutism, but concerns about the induction of hepato cellular dysfunction preclude its use. Finasteride is a competitive inhibitor of 5α-reductase type 2. Beneficial effects on hirsutism have been reported, but the predominance of 5α-reductase type 1 in the PSU appears to account for its limited efficacy. Finaste ride would also be expected to impair sexual differentiation in a male fetus, and it should not be used in women who may become pregnant. Although studies of dutasteride are limited in number, it appears that this agent may have efficacy in treating scalp hair thinning and loss as well as hirsutism. Dutasteride differs from finasteride as it targets both 5α-reductase types 1 and 2. Ultimately, the choice of any specific agent(s) must be tailored to the unique needs of the patient being treated. As noted previously, pharmacologic treatments for hirsutism should be used in conjunc tion with nonpharmacologic approaches. It is also helpful to review the pattern of female hair distribution in the normal population to dispel unrealistic expectations. ■ ■FURTHER READING Azarchi S et al: Androgens in women: Hormone-modulating thera pies for skin disease. J Am Acad Derm 80:1509, 2019. Brown DL et al: Ovarian stromal hyperthecosis: Sonographic features and histologic associations. J Ultrasound Med 28:587, 2009. Forslund M et al: Different kinds of oral contraceptive pills in poly cystic ovary syndrome: A systematic review and meta-analysis Eur J Endocrinol 189:S1, 2023. Haak CS et al: Hair removal in hirsute women with normal testoster one levels: A randomized controlled trial of long-pulsed diode laser vs. intense pulsed light. Br J Dermatol 163:1007, 2010. Martin KA et al: Evaluation and treatment of hirsutism in premeno pausal women: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 103:1233, 2018. McCartney CR, Marshall JC: Polycystic ovary syndrome. N Engl J Med 375:1398, 2016. Rosenfield RL, Ehrmann DA: The pathogenesis of polycystic ovary syndrome (PCOS): The hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 37:467, 2016.

Revision #1
Created 2026-01-06 16:35:18 UTC by Omar Ayman
Updated 2026-01-06 16:35:18 UTC by Omar Ayman