Polycystic Ovary Syndrome

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7.1 Introduction

Polycystic ovary syndrome (PCOS) remains an enigmatic condition that classically presents as oligomenorrhea in the context of hyperandrogenism and obesity. The metabolic features include insulin resistance, dyslipidemia, and obesity. The widespread availability of ultrasonography has fostered the notion that there is a classical ovarian morphology with increased ovarian size and stroma and a cortical ring of follicles often referred to as a "pearl necklace". The advent of anti-Müllerian hormone (AMH) assay has confirmed an increase in oocyte count. Importantly, the presentation and recognition of PCOS changes with age due to oocyte depletion. Postmenopausal persistence of ovarian stromal and theca leads to a related condition referred to as hyperthecosis.

Clinical Case

A 25-year-old woman with irregular periods since puberty wishes to discuss her weight problem and its potential impact on her future fertility. She is not interested in fertility at this moment. She has tried different methods for weight loss unsuccessfully. She has some increased facial and body hair that has slightly increased with time. She is presently in a relationship and wants contraception. Her body mass index reveals a body mass index (BMI) of 31.

7.2 Diagnostic Criteria

Multiple professional organizations offer criteria for the diagnosis of PCOS. Indeed, a recent NIH consensus conference suggesting that the syndrome should be renamed lead to a debate that continues without resolution about the criteria for the diagnosis of PCOS. The 1990 NIH conference on PCOS suggested diagnostic criteria of hyperandrogenism and/or hyperandrogenemia, chronic anovulation, and exclusion of other known disorders [1]. In 2003, a PCOS consensus workshop in Rotterdam sponsored by the European Society of Human Reproduction and Embryology (ESHRE)/American Society of Reproductive Medicine (ASRM) revised the diagnostic criteria for PCOS [2]. The revised criteria state that PCOS remains a diagnosis of exclusion, but that two out of the following three criteria must be present: (1) oligo- or anovulation, (2) hyperandrogenism and/or hyperandrogenemia, and (3) polycystic ovaries. A polycystic ovary is defined as having 12 or more follicles in one ovary measuring 2–9 mm in diameter, and/or increased ovarian volume of greater than 10 mL, which is the maximum size of a normal ovary (Fig. 7.1). Administration of oral contraceptive pills and the presence of follicles >10 mm modify ovarian morphology; thus, the definition of a polycystic ovary does not apply to these clinical scenarios.

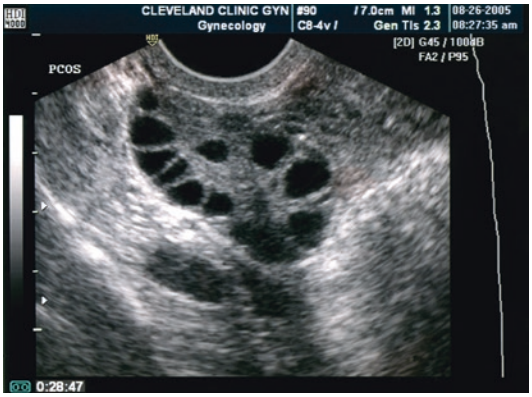

Fig. 7.1 This is the classical image of PCOS with an enlarged ovary containing an increased number of small follicles around the periphery of the cortex, resembling a string of pearls, along with a bright echogenic stroma

The differential diagnosis should include other causes of hyperandrogenism and oligomenorrhea such as nonclassical congenital adrenal hyperplasia (CAH), hypothalamic hypogonadism, Cushing's syndrome and disease, hyperprolactinemia, thyroid disease, acromegaly, androgen-secreting neoplasms of the ovary or adrenal gland, and exogenous steroid use. The ontogeny of androgen profiles has been described in a Nordic multicenter collaborative study. Women with PCOS also had elevated serum androgen levels after menopause. In the absence of high sensitivity and high specificity testosterone assays, the best predictive hormone was androstenedione [3].

7.3 Prevalence

The prevalence of PCOS is estimated to be 4–12% of reproductive-age women. The largest US study on PCOS prevalence was published in 1998 [4]. Out of 277 women included in the study, 4.0% had PCOS as defined by the 1990 NIH criteria. The prevalence was 4.7% for white women and 3.4% for black women. The inclusion of polycystic ovaries in the 2003 Rotterdam criteria calls for reevaluation of the prevalence of PCOS, as 21–23% of normal women have polycystic-appearing ovaries on ultrasound.

7.4 Clinical Case

7.4.1 Hyperandrogenism

Clinical manifestations of hyperandrogenemia include hirsutism, acne, and male pattern alopecia. Hirsutism is defined as the growth of coarse, pigmented hairs in androgen-dependent areas such as the face, chest, back, and lower abdomen. Approximately 80% of hirsute patients will have PCOS [5]. The modified Ferriman–Gallwey scoring system can be used for clinical assessment of hirsutism. This system, which was originally used in the United Kingdom for a population of presumably Caucasian women, scores hair growth in nine body areas from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth) [6]. Other hyperandrogenic manifestations commonly found in PCOS patients include acne and alopecia [7, 8]. Acne is a result of androgen stimulation of the pilosebaceous unit with increased skin oiliness [7].

7.4.2 Obesity

Obesity is very common in PCOS, with the android pattern present in approximately 44% of women with PCOS [9]. This central obesity is more characteristic of PCOS, as these patients have an increased waist-to-hip ratio compared to obese women without PCOS [10]. Hyperinsulinemia may stimulate central adiposity, which, in turn, exacerbates underlying or latent insulin resistance [11].

7.4.3 Insulin Resistance, Diabetes, and Acanthosis Nigricans

Insulin resistance and diabetes are important health concerns commonly seen in association with polycystic ovarian syndrome and will be discussed at length later in this chapter. Acanthosis nigricans is a dermatological condition of hyperkeratosis and increased skin pigmentation with raised, symmetrical, darkened, velvety plaques that commonly appear on the nape of the neck. It can also be found in the axilla, groin, and other intertriginous areas of the body. Elevated insulin has a mitogenic effect on basal cells of the epidermis, making acanthosis nigricans a relatively specific clinical marker of insulin resistance [12].

7.4.4 Irregular Menses and Infertility

Some of the menstrual abnormalities seen with chronic anovulation include secondary amenorrhea, oligomenorrhea, and dysfunctional uterine bleeding. Menarche typically begins at a normal or early age, but the menstrual irregularities often seen in adolescents may never resolve for the PCOS patient. The irregular menses may be masked in PCOS patients if they are on oral contraceptives. PCOS is the most common cause of anovulatory infertility, which often serves as the impetus for the patient to seek medical attention. Patients may report false-positive urinary ovulation predictor tests due to chronic elevation in luteinizing hormone (LH).

7.4.5 Miscarriage

The risk of a first-trimester spontaneous abortion is reported to be significantly higher for patients with PCOS. The spontaneous abortion rate in PCOS is reported to be 30% [13]. In comparison, retrospective studies find the risk of spontaneous abortion to be 5–14% for normal women [14, 15]. Of patients with recurrent miscarriage, 36–82% have polycystic ovaries [13, 16, 17].

Several explanations have been offered. For example, Homburg et al. demonstrated that high concentrations of LH during the follicular phase in women with polycystic ovaries have a deleterious effect on rates of conception and are associated with early pregnancy loss [18].

7.5 Pathogenesis

7.5.1 Altered Gonadotropin Secretion

One of the well-described features of PCOS is an increase in LH and relative decrease in follicle-stimulating hormone (FSH) [19]. The relative decrease in FSH is the chief cause of anovulation. The pulsatile secretion of LH from the pituitary is increased in amplitude and frequency [20]. In addition, the pituitary has a greater LH response to gonadotropin-releasing hormone (GnRH) compared with normal women [20, 21].

The pulsatile secretion of GnRH cannot be studied in humans, so it must be inferred by detecting peripheral LH patterns. A study of PCOS women by Berga et al. found increased pulse frequency and amplitude for LH and α (alpha)-subunit, providing evidence for aberrant increases in GnRH pulse frequency (Fig. 7.2) [20]. Elevated LH is not caused by altered pituitary sensitivity to GnRH, as GnRH receptor blockade resulted in similar LH decreases in PCOS and normal women [22]. These findings suggest a derangement of the hypothalamic–pituitary axis, which appears to play a major role, because many of the cardinal features of PCOS can be traced to alterations in gonadotropins.

7.5.2 Neuroanatomical Considerations

The GnRH pulse generator refers to the synchronized pulsatile secretion of GnRH from neurons that are widely distributed in the medial basal hypothalamus. Knobil and associates conducted experiments with the Rhesus monkey to establish that the GnRH system exhibits rhythmic electrical behavior in the arcuate nucleus of the

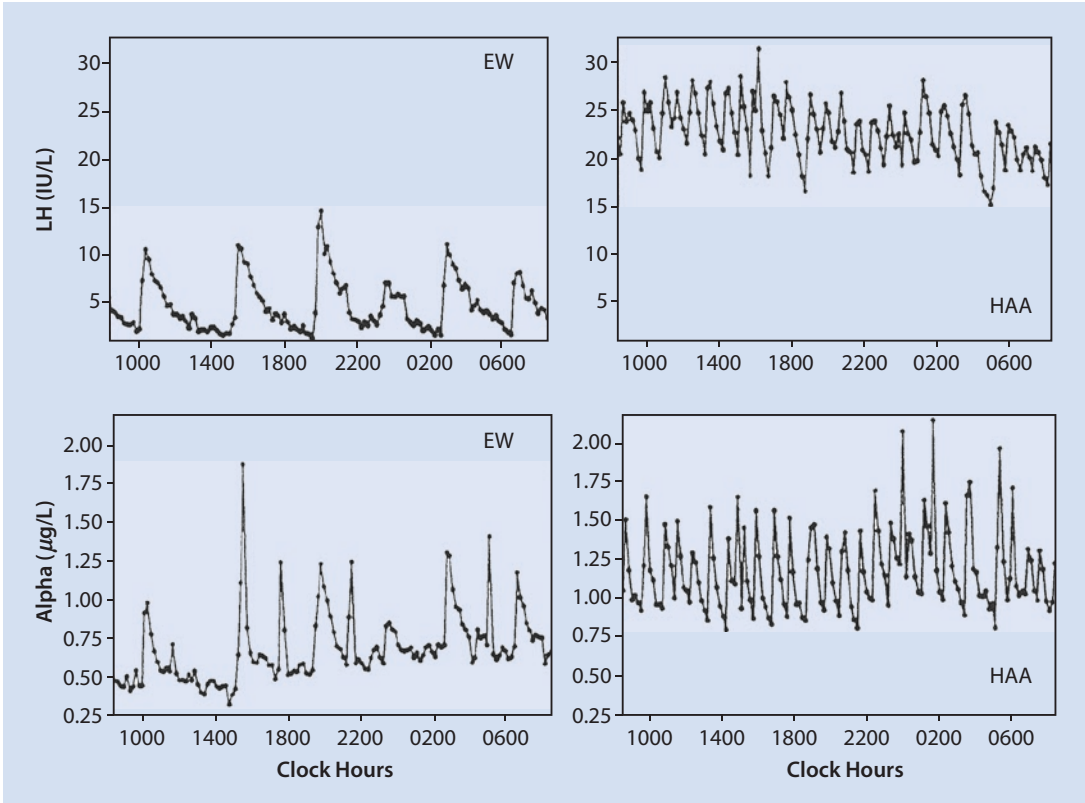

Fig. 7.2 Twenty-four hour concentration profiles of LH (*top*) and α(alpha)-subunit (*bottom*) in an eumenorrheic woman (EW) (*left*), studied in the follicular phase (day 2) and in a woman with hyperandrogenic anovulation (HAA)/PCOS (*right*). Reprinted with permission from Berga S, Guzick D, Winters S. Increased luteinizing hormone and alpha-subunit secretion in women with hyperandrogenic anovulation. J Clin Endocrinol Metab 1993; 77(4):895–901. Copyright 1993, The Endocrine Society

medial basal hypothalamus [23]. There was remarkable synchrony between pulses of GnRH in the portal blood and LH pulses in peripheral blood. This phenomenon was later studied in isolated human medial basal hypothalamus, where GnRH pulses were found to occur at a frequency of 60–100 min [24].

The secretion of GnRH into the portal vasculature also appears to be regulated by dynamic remodeling of GnRH neurovascular junctions. Morphological plasticity of the median eminence during the menstrual cycle has been demonstrated, where the maximal number of GnRH neuro-vasculature junctions are found during the LH surge [25].

7.5.3 GnRH Neuroregulation in PCOS

The GnRH pulse generator in PCOS patients is intrinsically faster, and the frequency is less likely to be suppressed with continuous estrogen and progesterone treatment [26].

Increased central adrenergic tone has been implicated as a cause of the aberrations of GnRH and gonadotropin secretion in PCOS. One possible mechanism is the increase in local blood flow and permeability of the portal vascular system, permitting the entry of increased amounts of GnRH [27]. Dopamine injection into the third ventricle led to a rapid increase in GnRH and prolactin inhibitory factor in portal blood, suggesting dopamine-mediated regulation of GnRH and prolactin inhibitory factor [28]. The identification of β(beta)-1-adrenergic and D1-dopaminergic receptors on GT-1 GnRH neurons provides a mechanism by which norepinephrine and dopamine could regulate gonadotropin release via direct synapses on GnRH neurons [29].

The role of insulin-like growth factor 1 (IGF-1) in modulation of GnRH cells has also been investigated. IGF-1 regulates growth, differentiation, survival, and reproductive function. The IGF receptor is a tyrosine kinase receptor located in the periphery and CNS, including the median eminence [30]. In PCOS women, an increased ratio of IGF-1 to their binding proteins correlated significantly with increased concentrations of circulating LH [21]. These findings suggest that IGF-1 can modulate GnRH neurons by inducing gene expression, resulting in more circulating LH.

7.5.4 Hyperandrogenemia

Circulating androgens are elevated in PCOS, with contributions from the ovary and adrenal glands. The elevated androgens can only be partially suppressed with combined oral contraceptive (COC) therapy. Daniels and Berga treated PCOS women with 3 weeks of COCs and found that androstenedione levels remained significantly higher compared to treated controls [26]. Pulse frequency of LH was suppressed in both PCOS women and controls, but the frequency remained significantly higher in PCOS patients (Fig. 7.3). This suggests there is reduced sensitivity of the GnRH pulse generator to suppression by sex steroids. The authors also suggest that GnRH drive in PCOS women may be intrinsically and irreversibly faster than in eumenorrheic women.

7.5.5 Theca Cell Function

Ovarian hyperandrogenism is driven by LH acting on theca cells, and the effect is amplified by the increased sensitivity of PCOS theca cells to LH [31]. Hyperandrogenism may also result from dysregulation of the androgen-producing enzyme P450c17, which has 17 α (alpha)-hydroxylase and 17,20-lyase activities. In contrast, in vivo studies do not find significant increases in androgen secretion in women with PCOS or normal women, despite considerable increases in insulin levels. A role for insulin is strongly suggested by the observation that reduction of hyperinsulinemia is associated with decreases of serum androgens. Treatment of PCOS patients with metformin, which reduces hepatic glucose production and secondarily lowers insulin, has been shown to decrease levels of testosterone, DHEAS, and androstenedione [32].

7.5.6 Adrenal Function

Excess adrenal androgen production is seen in PCOS women, with a 48–64% increase in DHEAS and 11β (beta)-hydroxyandrostenedione. The underlying cause of elevated adrenal androgens is yet to be elucidated, but PCOS women do not

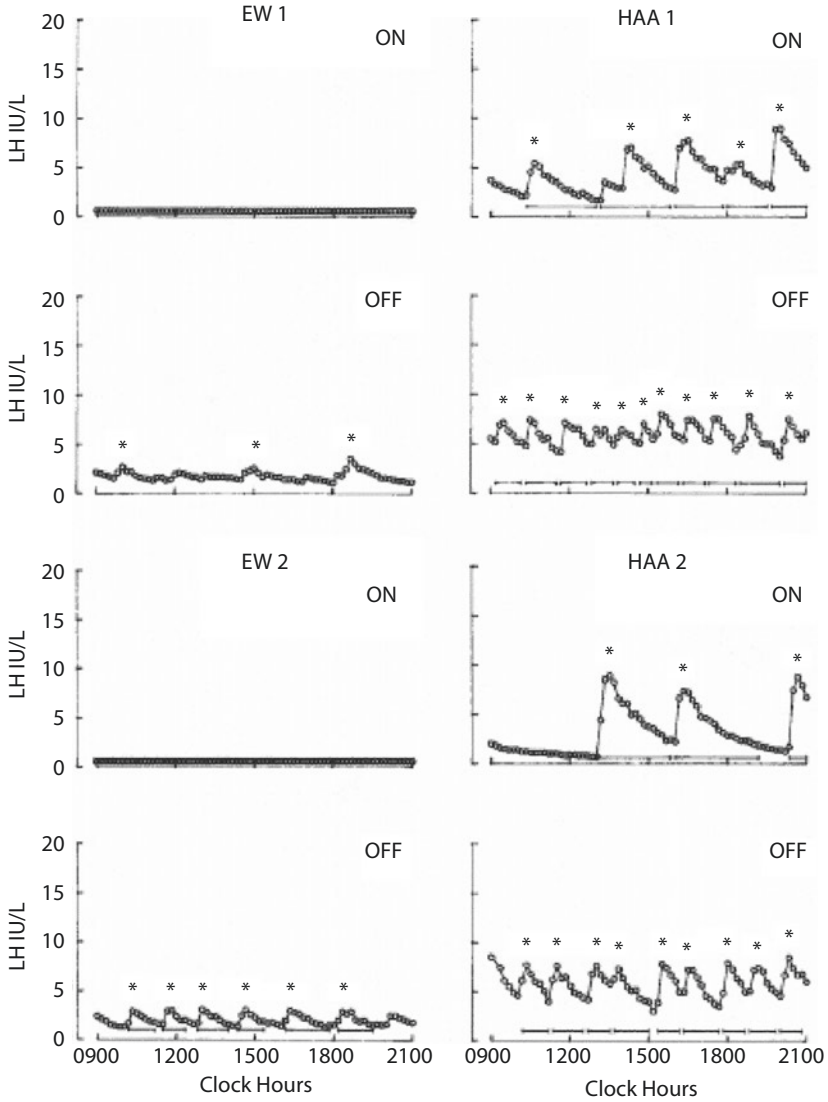

Fig. 7.3 Representative 12-h pulse patterns in two women with polycystic ovary syndrome/HAA are shown on the *right side* and those from eumenorrheic women on the *left*. "ON" means subjects were studied on day 21 of a combined oral contraceptive containing 35 μg of ethinyl estradiol and 1 mg of norethindrone. "OFF" refers to day 7 following cessation of the combined oral contraceptive. Reprinted with permission from Daniels T, Berga S. Resistance of gonadotropin releasing hormone drive to sex steroid-induced suppression in hyperandrogenic anovulation. J Clin Endocrinol Metab 1997; 82(12):4179–4183. Copyright 1997, The Endocrine Society

have increased adrenocorticotropic hormone (ACTH) levels [33]. Increased adrenal androgen production in PCOS is likely caused by either altered adrenal responsiveness to ACTH or abnormal adrenal stimulation by factors other than ACTH.

7.5.7 Anovulation

The cause of anovulation in PCOS patients has yet to be clarified. However, several observations in granulosa function have been described that may give insight into this process.

7.5.8 Granulosa Cell Function

FSH levels are characteristically low in PCOS women, resulting in arrested follicular development. Insufficient granulosa cell aromatase activity was the basis of earlier studies that tried to explain poor follicular development, as follicular fluid estradiol concentrations were thought to be low. To the contrary, more recent studies found that PCOS granulosa cells are hyperresponsive to FSH in vitro, and estradiol concentrations from PCO follicles and normal follicles are no different [34]. A dose response study in PCOS women demonstrated a significantly greater capacity for estradiol production in response to recombinant human FSH compared with normal women [35]. The incremental response of serum estradiol was almost two times greater and considerably accelerated compared with that found in normal women.

7.5.9 Insulin Resistance

Although 50–70% of PCOS patients have insulin resistance [36], it is not one of the diagnostic criteria of PCOS. The topic deservedly receives much attention, as many of the clinical signs and symptoms of PCOS may be attributed to excess insulin exposure. The precise molecular basis for insulin resistance is unknown, but it appears to be a postreceptor defect [37]. There is tissue specificity of insulin resistance in PCOS: muscle and adipose tissue are resistant, while the ovaries, adrenals, liver, skin, and hair remain sensitive. The resistance to insulin in skeletal muscle and adipose tissue leads to a metabolic compromise of insulin function and glucose homeostasis, but there is preservation of the mitogenic and steroidogenic function in other tissues. The effect of hyperinsulinemia on the sensitive organs results in downstream effects seen in PCOS, such as hirsutism [5], acanthosis nigricans [12], obesity [11], stimulation of androgen synthesis, increase in bioavailable androgens via decreased sex hormone-binding globulin (SHBG) [38], and, potentially, modulation of LH secretion.

In 1992, Hales and Barker proposed the concept that the environmental influence of undernutrition in early life increased the risk of type 2 diabetes in adulthood [39]. They discovered a relationship between low birth weight and type 2 diabetes in men from England. In the "thrifty phenotype hypothesis," malnutrition serves as a fetal and infant insult that results in a state of nutritional thrift. The adaptations result in postnatal metabolic changes that prepare the individual for survival under poor nutritional conditions. The adaptations become detrimental when the postnatal environment changes to one of an overabundance of nutrients, resulting in obesity and diabetes.

Insulin resistance is a component of the World Health Organization (WHO) definition of the metabolic syndrome, which is a cluster of risk factors for cardiovascular disease [40]. The WHO defines the metabolic syndrome as the presence of glucose intolerance or insulin resistance, with at least two of the following: hypertension, dyslipidemia, obesity, and microalbuminuria. Women with PCOS are 4.4 times more likely to have the metabolic syndrome, so it becomes prudent to screen these patients, especially in those with insulin resistance [41].

Lipid abnormalities are also more prevalent in PCOS patients. There can be a significant increase in total cholesterol, LDL cholesterol, and triglycerides, and a decrease in HDL cholesterol compared to weight-matched controls [42]. The dyslipidemia, impaired glucose intolerance, central obesity, hyperandrogenism, and hypertension seen in PCOS patients greatly increase the risk for cardiovascular disease. Based on this risk profile, women with PCOS have a sevenfold increased risk of myocardial infarction [43].

7.5.10 Laboratory Evaluation

In addition to confirming elevations of androgens, the laboratory evaluation of PCOS should have the objective of excluding other causes of hyperandrogenic anovulation. Androgen-producing tumors of the ovary and adrenals must be excluded. The adrenal glands contribute 98% of circulating DHEAS, while both the ovaries and adrenals contribute equal amounts of circulating testosterone and androstenedione. If total testosterone is greater than 200 ng/dL or DHEAS is greater than 7000 ng/dL, MRI is warranted to identify the hormone-secreting lesion. Measuring 17 α (alpha)-hydroxyprogesterone will screen for 21-hydroxylase deficiency, the most common enzyme deficiency in

nonclassical CAH. A 17-hydroxyprogesterone level of greater than 3 ng/mL is defined as elevated and should be followed by an ACTH stimulation test, using 250 μg of synthetic ACTH given intravenously following an overnight fast. A 1-h increase of 17 α (alpha)-hydroxyprogesterone of more than 10 ng/mL is indicative of an enzyme defect in 21-hydroxylase.

Cushing's syndrome may masquerade as PCOS. Those who have additional signs of Cushing's syndrome, such as a moon facies, buffalo hump, abdominal striae, easy bruising, and proximal myopathy, should undergo screening with a 24-h urinary-free cortisol. In the work-up for anovulation, exclusion of prolactinoma should be performed. It is not uncommon to detect mild elevations in prolactin levels in PCOS patients. Thyroid-stimulating hormone (TSH) should be evaluated. LH, FSH, and estradiol levels should be obtained to exclude hypothalamic amenorrhea or premature ovarian failure.

7.5.11 Diabetes Screen/Evaluation of Insulin Resistance

The 2003 Rotterdam PCOS consensus group recommends a 2-h oral glucose tolerance test (OGTT) for obese PCOS patients and nonobese PCOS patients with risk factors for insulin resistance, such as family history of diabetes [2]. Defining insulin resistance is difficult, because the concept is nebulous with no universally accepted diagnostic strategy. The WHO defines insulin resistance as the lowest quartile of measures of insulin sensitivity. Women with PCOS are at significantly increased risk for impaired glucose tolerance and type 2 diabetes compared to age-, weight-, and ethnicity-matched controls [44]. If either the fasting glucose is 126 mg/dL or more, or the 2-h level is 200 mg/dL or more, diabetes is detected and should be confirmed with a repeat test. Impaired fasting glucose is defined as a glucose level between 100 and 126 mg/dL. Impaired glucose tolerance is defined as a 2-h glucose level between 140 and 200 mg/dL. It is also reasonable to obtain a fasting lipid profile in women suspected of having risk factors for cardiovascular disease. HgbA1C has been recently advocated as an accurate screening tool in evaluation of insulin resistance and diabetes in women with PCOS [45].

7.5.12 Treatment

There are many considerations when deciding on therapy for PCOS (Fig. 7.4). Identification of patient concerns is necessary when prioritizing goals and formulating a treatment plan. A combination of therapies may be warranted, and the practitioner should appropriately counsel the patient on the treatment expectations. Amelioration of long-term health risks should be emphasized, regardless of the primary complaints of the patient.

7.5.13 Weight Loss

Weight reduction should be a major component of any treatment plan for the overweight patient (BMI >25). Any sustained improvement in weight should involve diet and exercise, and consultation with a nutritionist may be helpful for those with difficulty achieving weight reduction. Obese PCOS patients who achieve weight loss will have an increase in SHBG, decrease in free testosterone, and improvement in fasting insulin levels [46].

7.5.14 Oral Contraceptives

Combination oral contraceptives have been the mainstay of PCOS management for the patient not interested in conception. Contraceptives suppress pituitary LH and consequently reduce ovarian androgen secretion, increase SHBG, and reduce free testosterone, while regulating menses and reducing the risk of endometrial hyperplasia or malignancy. However, there may be mild attenuation of insulin sensitivity.

Korytkowski et al. have shown that short-term use of COCs in PCOS women results in a small decrease in insulin sensitivity and no change in the baseline elevation in triglyceride levels [47]. However, in normal women, COCs were shown to have an even more pronounced decline in insulin sensitivity, along with a significant elevation in triglyceride levels. The long-term effects of COCs upon insulin sensitivity and lipoprotein profiles have not been well documented. PCOS women are at greater risk for the development of diabetes and cardiovascular disease; thus, further investigation into the safety of long-term hormonal therapy is needed.

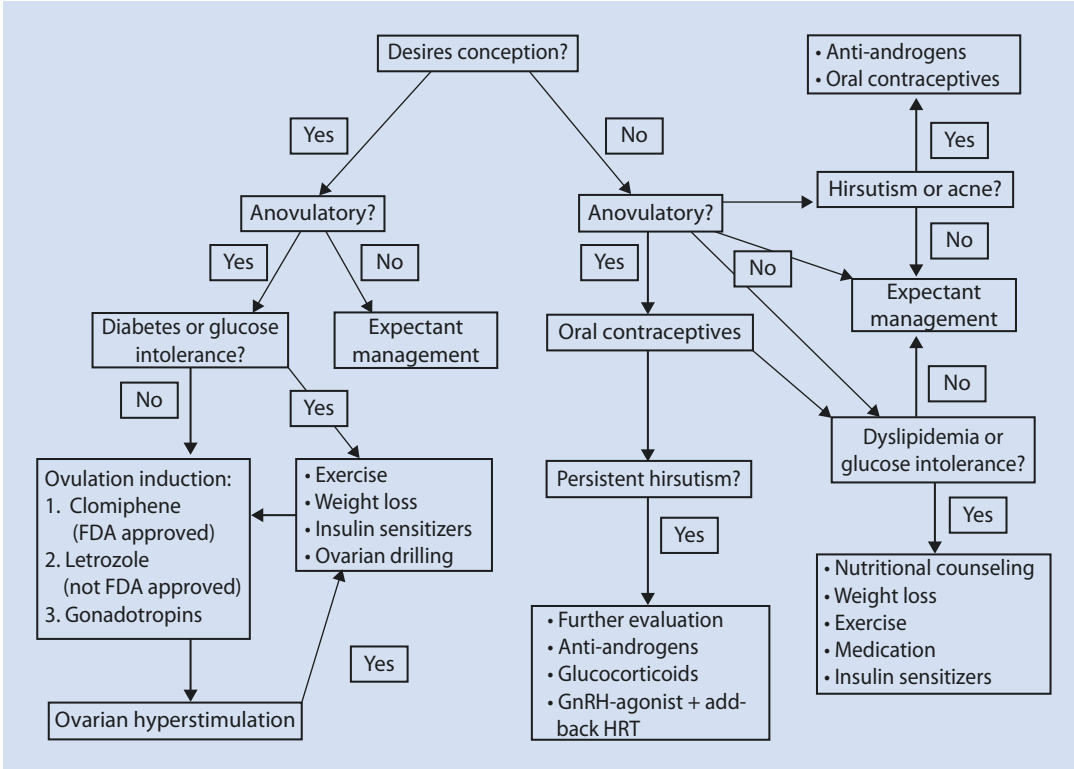

Fig. 7.4 Polycystic ovary syndrome treatment algorithm. Reprinted from Am J Obstet Gynecol, 179/6S, Berga S, The obstetrician-gynecologist's role in the practical management of polycystic ovary syndrome, 109S–113S, Copyright 1998, with permission from Elsevier. Letrozole can also be used for ovulation induction although it is not FDA approved

7.5.15 Hair Removal

In women with significant hirsutism, removal of unwanted hair, especially on the face, chest, and abdomen, is often an important concern. Shaving, plucking, waxing, and depilatories are the most common approaches used for temporary removal. These approaches do not induce coarser or faster hair growth, but must be repeated at frequent intervals.

Electrolysis is probably the most commonly used technique for permanent hair removal, wherein a fine needle is inserted into each hair follicle and an electrical current is applied. Hair follicles must be treated individually and several treatments may be needed to destroy the follicle. Usually, repeated treatments are required over a 12- to 18-month period. Possible side effects include pain, infection, hyper- or hypopigmentation, and keloid formation in susceptible women. Laser hair removal techniques, and the related intense pulsed light devices, are other options for hair removal. These techniques work by emitting light at various wavelengths, energy output, and pulse widths that are selectively absorbed by darker structures. For this reason, laser hair removal works best for light-skinned people with dark hair. As with electrolysis, laser treatments for hair removal must be repeated.

7.5.16 Topical Eflornithine Hydrochloride

Eflornithine hydrochloride (Vaniqa, Bristol-Myers Squibb, New York, NY) is a prescription-only topical cream approved by the FDA for reducing and inhibiting the growth of unwanted facial hair. This drug works by irreversibly inhibiting ornithine decarboxylase, an enzyme that facilitates cell division in hair follicles. The cream is applied twice a day to areas of unwanted facial hair, and <1% is absorbed systemically. It is designated by the FDA as a Pregnancy Category C drug.

Noticeable results are usually observed after 4–8 weeks of therapy. Application must be continued for as long as inhibition of hair growth is desired, although facial hair growth is reduced for up to 8 weeks after discontinuation.

7.5.17 Antiandrogens

Antiandrogens are commonly used as an adjunct to oral contraceptive therapy for treatment of hirsutism, but they have also been found to improve ovulation and restore regular menses. It is important to remember that all antiandrogens are teratogenic and pose a risk of feminizing a male fetus, and thus should be used along with an effective form of contraception.

Spironolactone is an aldosterone antagonist, and it is the most commonly used adjunctive agent in the treatment of hirsutism. It competes for testosterone binding sites on the pilosebaceous unit, inhibits 5α (alpha)-reductase, and inhibits androgen production by interfering with cytochrome P450 [48]. The potassium-sparing effect warrants judicious use in the patient on potassium supplementation or preexisting hypertension.

Flutamide is a nonsteroidal antiandrogen that competes for the androgen receptor. Anovulatory PCOS patients treated with flutamide experienced resumption of ovulation with restoration of normal ovarian appearance with one dominant follicle [49]. This study also reported a reduction in plasma levels of LH, androstenedione, and testosterone. Liver toxicity is a rare but potentially serious side effect of flutamide.

Finasteride is a potent inhibitor of 5α (alpha)-reductase used for the treatment of prostatic hyperplasia with promising results as a treatment for hirsutism. All antiandrogens should be used along with a form of contraception, because they are teratogenic and pose a risk of feminizing a male fetus.

7.5.18 Insulin-Sensitizing Agents

Insulin-sensitizing agents have been shown to improve endocrine and reproductive abnormalities in PCOS. Metformin is the most thoroughly investigated insulin-lowering agent used in PCOS. It is a biguanide that primarily works by suppressing hepatic gluconeogenesis and, to a lesser degree, increases peripheral insulin sensitivity [50]. Thiazolidinediones (TZDs) are peroxisome proliferator activating receptor [PPAR-γ(gamma)] agonists that improve peripheral insulin sensitivity but do not appear to have an effect on hepatic glucose production [50]. This class of medications includes troglitazone, pioglitazone, and rosiglitazone.

Troglitazone is the oldest but was removed from the market in 2000 owing to hepatotoxicity. Rosiglitazone and pioglitazone are still available and appear to be safer. The role of insulin-sensitizing agents is still an area of active investigation.

Many studies have demonstrated the positive effects of metformin on the reproductive axis of PCOS patients, with one of the most comprehensive studies recently demonstrating a dramatic improvement after 6 months of treatment. Metformin administration to nonobese hyperandrogenic PCOS patients resulted in a reduction of (1) LH pulse amplitude; (2) androstenedione levels; (3) testosterone levels; (4) ovarian volume; and (5) Ferriman–Gallwey scores. Menstrual cyclicity was also improved in most patients [51]. The investigators did not determine if metformin increased the likelihood of ovulation or if FSH levels rose. Similarly, troglitazone-treated PCOS patients demonstrated improved ovulation, decreased hirsutism, decreased free testosterone, and increased SHBG [52].

Insulin-sensitizing agents have a favorable effect on hyperandrogenism by reducing LH secretion, thereby removing the main stimulus for pathologic ovarian and adrenal androgen production. The reduction in insulin levels elevates hepatic SHBG production, decreasing free androgen levels. The concurrent improvement in hyperinsulinemia and hyperandrogenemia conferred by the use of insulin-sensitizing agents may ameliorate hirsutism.

The improvement in ovulation and menstrual cyclicity in patients treated with insulin-sensitizing agents suggests improved fertility. Indeed, spontaneous and clomid-induced ovulation rates in metformin-treated women with PCOS are increased [53]. Spontaneous ovulation occurred in 34% of those treated with 500 mg of metformin three times daily compared to only 4% in the placebo group. Clomid-induced ovulation occurred in 90% of women who received metformin compared to 8% who received placebo. For those who are clomiphene-resistant, significant improvements in ovulation and pregnancy rates

were reported in a randomized, double-blind, placebo-controlled trial for women pretreated with metformin [54]. Troglitazone alone and the combination of troglitazone plus clomiphene is also associated with increased rates (gamma) of ovulation and pregnancy in insulin-resistant women with PCOS [55]. One recent study found that in escalating doses letrozole was more effective than clomiphene as a fertility treatment in women with the polycystic ovary syndrome. Ovulation, conception, pregnancy, and live birth were significantly more likely after treatment with letrozole. The rate of pregnancy loss, the mean pregnancy duration and birth weight, and rates of neonatal complications (including anomalies) did not differ significantly between the letrozole and clomiphene treatment groups [56].

Though metformin is a category B medication, its use throughout pregnancy is becoming more attractive. In one retrospective study, Jakubowicz et al. found a significant reduction in the rate of early pregnancy loss for PCOS women who conceived while taking metformin and continued the agent throughout pregnancy. The rate of early pregnancy loss in the metformin group was 8.8% compared to 41.9% in controls. In the women with a prior history of miscarriage, the early loss rate was 11.1% for the metformin group compared with 58.3% in the control group [57]. The efficacy of metformin for pregnancy loss is not yet clear, and safety data for this indication are lacking. In 2007, Legro et al. published a well-designed trial that concluded that live birth rate in PCOS patients prescribed clomiphene (22.5%) was superior to metformin alone (7.2%) and not dissimilar from combination clomiphene/metformin therapy (26.8%) [58].

Metformin should not be given to those with conditions associated with elevated lactate levels, such as renal or hepatic disease, as there is a risk of lactic acidosis with an associated mortality of 50% [59]. Although most studies of metformin in PCOS used a dose of 500 mg three times daily, no studies have been performed to determine the optimal dosing regimen for improvement in insulin sensitivity, reduction of androgens, and resumption of ovulation. A dose–response study of type II diabetic patients demonstrated that the 2000-mg daily dose was optimal for improvement of glucose homeostasis [60], but the relevance of this dose to the PCOS population remains to be investigated.

Metformin should be initiated in a stepwise approach, titrating the dose slowly over several weeks in order to minimize side effects. Most patients will experience gastrointestinal symptoms such as nausea, diarrhea, indigestion, and abdominal discomfort. Side effects will resolve in several days for most patients, which allows incremental dosing increases on a weekly basis up to a maximum dose of 1000 mg bid. Baseline serum creatinine should be obtained with yearly monitoring to avoid lactic acidosis.

There are no guidelines currently on the long-term use of metformin to prevent or improve health outcomes in patients with PCOS. One of the serious reactions of TZD is hepatotoxicity. Initiation of treatment requires baseline liver function studies along with periodic monitoring.

7.6 Ovarian Surgery

7.6.1 Ovarian Wedge Resection

Ovarian wedge resection is a surgical procedure used for PCOS patients that has been found to restore both regular menses and ovulation in the majority of cases. This procedure, originally performed by laparotomy, consisted of removing a wedge of ovarian tissue and reconstructing the ovary. Laparoscopic techniques for ovarian wedge resection have described.

The primary disadvantage of this approach is the formation of significant pelvic adhesions, which occurs in at least one-third of the patients. The concern is that these adhesions might actually decrease fertility and increase the risk of pelvic pain. Another concern is that the restoration of ovulation is unlikely to be permanent, since the ovaries are not the causal agents in this complex systemic disorder. However, the actual long-term effectiveness of wedge resection has never been reported.

7.6.2 Ovarian Drilling

A laparoscopic variant with similar results to ovarian wedge resection is called ovarian drilling. This procedure involves making multiple punctures in the ovarian cortex and destroying ovarian tissue using unipolar electrosurgery or laser. The

results and complications for this approach appear to be similar or slightly less than those for ovarian wedge resection, although a prospective randomized study has never been done. There are additional concerns about long-term effects of ovarian drilling on ovarian function.

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