Polycystic Ovary Syndrome: An Overview

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Topics in Advanced Practice Nursing eJournal 2(3), 2002.

Posted 07/30/2002

Abstract and Introduction

Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy that affects women. PCOS is also a leading cause of infertility. Women with PCOS may present with obesity, amenorrhea, oligomenorrhea, infertility, or androgenic features. Those with PCOS are also at increased risk for both diabetes and diabetic complications and cardiovascular disease, with a risk of a myocardial infarction 7 times the normal. We know that if patients with PCOS are screened for these diseases, many long-term complications can be prevented.

Introduction

PCOS affects 5% to 10% of women in their reproductive years and is the most common endocrinopathy affecting women.[1-3] Stein and Leventhal[4] first described PCOS in 1935. Our understanding of the pathophysiology of PCOS has dramatically changed since then; now, there is particular emphasis on its relationship with insulin resistance. PCOS is a chronic hyperandrogenic state that has many significant short-term and long-term implications for patients such as oligomenorrhea, amenorrhea, infertility, diabetes mellitus, cardiovascular disease, increased risk of endometrial cancer, and excessive body hair (hirsutism).

PCOS is characterized by the following: (1) a menstrual cycle that ranges from > 35 days or < 8 cycles/year to complete absence of menses (amenorrhea); (2) evidence of androgen excess, such as acne, hirsutism, alopecia, acanthosis nigricans, or increased androgen levels on laboratory testing; (3) all other causes of hyperandrogenism and anovulation have been excluded.[1] It is not essential that a woman have polycystic ovaries to have this syndrome. Therefore, polycystic ovaries, observed on ultrasound, are a *sign* of PCOS and not by themselves diagnostic of the disease. Polycystic ovaries are seen 67% to 86% of the time in patients who have PCOS.[1,3,5,6]

Pathophysiology

The endocrinologic abnormality of PCOS begins soon after menarche. Chronically elevated luteinizing hormone (LH) and insulin resistance are 2 of the most common endocrine aberrations seen in PCOS. The genetic cause of high LH is not known. It is interesting to note that neither an elevation in LH nor insulin resistance alone is enough to explain the pathogenesis of PCOS.[7-9] In vitro and in vivo evidence offer support that high LH and hyperinsulinemia work synergistically, causing ovarian growth, androgen production, and ovarian cyst formation.

Obesity, which is seen in 50% to 65% of PCOS patients, may increase the insulin resistance and hyperinsulinemia. One important caveat is that the correlation between hyperandrogenism and insulin resistance has been recognized in both obese and nonobese anovulatory women. Thus, it is important to realize that a nonobese patient may also have insulin resistance. However, the insulin levels in obese women are higher than their nonobese counterparts. Clinically, though, both groups will [6,7]

have evidence of hyperandrogenism and oligo-ovulation or anovulation.

Insulin resistance can be characterized as impaired action of insulin in the uptake and metabolism of glucose.[6] Impaired insulin action leads to elevated insulin levels, which causes a decrease in the synthesis of 2 important binding proteins: insulin-like growth factor binding protein (IGFBP-I) and sex hormone binding globulin (SHBG). IGFBP-I binds to IGFBP-II and SHBG binds to sex steroids, especially androgens. The triad of hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome appears in a subgroup of patients with PCOS.[6,10,11]

Acanthosis nigricans, a dark and hyperpigmented hyperplasia of the skin typically found at the nape of the neck and axilla, is a marker for insulin resistance. Acanthosis nigricans is usually found in about 30% of hyperandrogenic women. Figure 1 illustrates acanthosis nigricans evident in a patient's axilla.

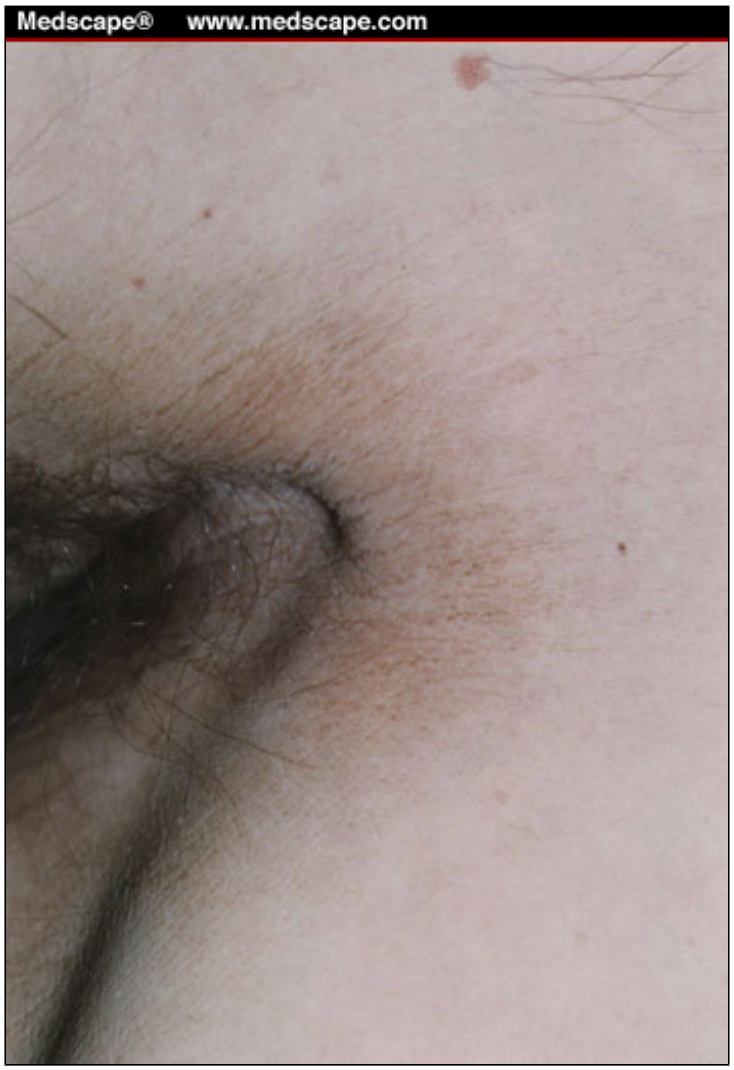


Figure 1. Acanthosis nigricans in a patient's axilla. Photo courtesy of Stanford Lamberg, MD, Associate Professor, Dermatology, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Relationship Between Diabetes Mellitus and PCOS

Women with PCOS are at higher risk of developing diabetes mellitus type 2 because of the relative insulin resistance. Also, these women tend to develop diabetes earlier in life, around the third or fourth decade. It is generally recommended, because of the known long-term complications of diabetes, that these young women be tested early in life and followed closely. These women should be screened in early pregnancy, as they have an increased risk of developing gestational diabetes.[2,5,12]

Relationship of Cardiovascular Disease to PCOS

Women who are hyperandrogenic and hyperinsulinemic are at increased risk for dyslipidemia, coronary artery disease, hypertension, and diabetes mellitus. The most common lipid abnormalities found in obese PCOS patients are decreased high-density lipoprotein and elevated triglycerides. In addition to the lipid abnormalities seen in women with PCOS, these patients are 7 times more likely to have a myocardial infarction.[3,13] Because cardiovascular disease is the leading cause of death of among women, prevention is essential.

Assessment of the PCOS Patient

History

In addition to obtaining a thorough medical and surgical history, elicit a completed menstrual history, including menarche and family history of PCOS. A history of hirsutism, acne, alopecia, menstrual irregularities, or infertility, especially in the patient's mother, is very important. A diagnosis of PCOS may often be made with a complete history. Pay particular attention to the onset of menstrual irregularities, as this will usually date back to menarche. Inquire about recent pregnancy status and other reproductive history such as miscarriages.

Medical history. A history of headaches or blurred vision (indicating pituitary tumor), any signs or symptoms of thyroid dysfunction (as a differential diagnosis of amenorrhea), or clinical signs of diabetes (indicating adrenal tumor) need to be elicited. Inquire about a history of acne, hirsutism, deepening of the voice, and increase in muscle mass (without exercise). If these symptoms have occurred, what has been tried to control them? It is imperative to know if the symptoms are recent or have occurred rapidly, either of which could indicate a virilizing syndrome or neoplasia. A rapid onset of these symptoms is rare in a PCOS patient, but if present, they suggest a need for an urgent work-up, as an ovarian tumor or adrenal tumor needs to be ruled out. Also, masculinization is uncommon with PCOS patients and is more suggestive of congenital adrenal hyperplasia.

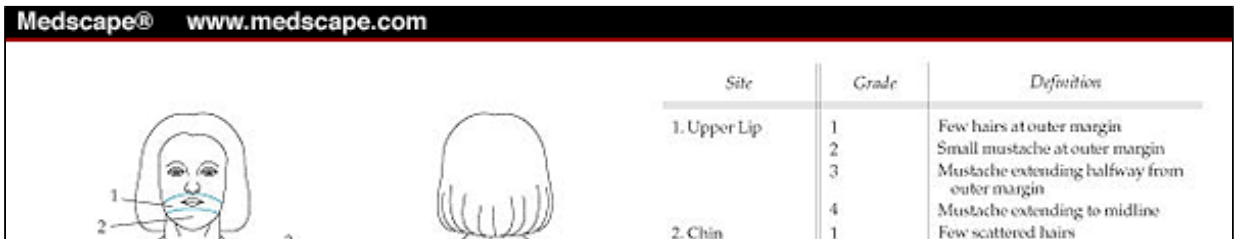
Family history. PCOS tends to run in families; it is important to ask about family history. Some believe that if a mother has PCOS and her daughter is showing signs of it, she should be evaluated by her pediatrician or by an endocrinologist.[14]

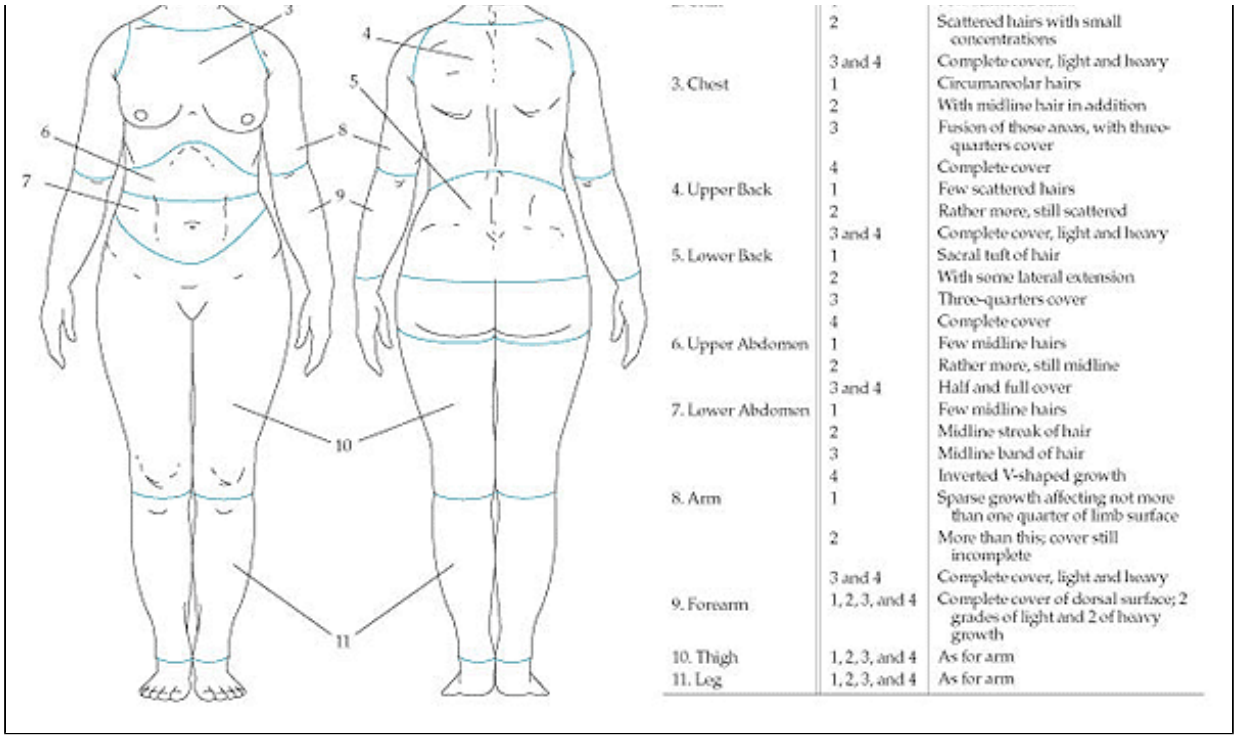
Social/cultural history. Ethnic factors must be considered in the evaluation of women who are hirsute. Northern European white women and women from Asia usually have small amounts of hair on their face, torso, and extremities. However, Mediterranean white women will frequently have hair on their upper lip, chin, and have dark hair on their arms and legs. Also, certain conditions like pregnancy and menopause can cause transient hirsutism. An important caveat to remember is the patient may not appear hirsute at the time of the examination as she may be using cosmetic procedures like waxing, shaving, or electrolysis to control it.

Medications. In addition to asking about the patient's current medications it is important to remember that there are certain medications and classes of medications that can cause transient hirsutism. Examples of these are phenytoin (*Dilantin*), diazoxide, glucocorticoids, and the phenothiazines.[1,9,15,16]

Clinical Features

Evaluate the skin for evidence of hirsutism, acne, alopecia, fat distribution, and pigment changes in the skin, specifically acanthosis nigricans. Hirsutism can be defined as hair in locations in women where it is usually not found. Examples of these locations are upper lip, chin, midline of the body, and in the intermammary region. Hirsutism can be graded using the Ferriman-Gallowey scoring system (Figure 2). This scoring system evaluates 9 key anatomic sites. These sites can be graded from 0 (no terminal hair growth) to 4 (maximal growth). The maximum score is 36. A score of 8 or greater suggests an androgen excess.[1,9,15]





	2	Scattered hairs with small concentrations
	3 and 4	Complete cover, light and heavy
3. Chest	1	Circumareolar hairs
	2	With midline hair in addition
	3	Fusion of these areas, with three-quarters cover
	4	Complete cover
4. Upper Back	1	Few scattered hairs
	2	Rather more, still scattered
	3 and 4	Complete cover, light and heavy
5. Lower Back	1	Sacral tuft of hair
	2	With some lateral extension
	3	Three-quarters cover
	4	Complete cover
6. Upper Abdomen	1	Few midline hairs
	2	Rather more, still midline
	3 and 4	Half and full cover
7. Lower Abdomen	1	Few midline hairs
	2	Midline streak of hair
	3	Midline band of hair
	4	Inverted V-shaped growth
8. Arm	1	Sparse growth affecting not more than one quarter of limb surface
	2	More than this; cover still incomplete
	3 and 4	Complete cover, light and heavy
9. Forearm	1, 2, 3, and 4	Complete cover of dorsal surface; 2 grades of light and 2 of heavy growth
10. Thigh	1, 2, 3, and 4	As for arm
11. Leg	1, 2, 3, and 4	As for arm

Figure 2. Ferriman-Gallowey scoring system for hirsutism. Reproduced with permission of publisher from Barbieri RL: V Polycystic Ovary Syndrome. 16 Women's Health. WebMD Scientific American® Medicine Online. Dale DC, Federman DD, Eds. WebMD Corporation, New York, 2002. http://www.samed.com

Even when a PCOS patient has increased levels of androgens, hirsutism may not be present unless there is an increase in peripheral androgen metabolism. This is why some women with PCOS are hirsute and others are not. Temporal balding is usually seen after prolonged exposure to androgens. Frontal balding is associated with a virilizing ovarian or adrenal tumor.

Central obesity with a hip ratio of > 0.85 is associated with cardiovascular disease and is a marker for PCOS. A "buffalo hump" on the back or purple striae on the abdomen might suggest Cushing's syndrome.

During the pelvic examination, assess for clitoromegaly and pelvic masses. Bilateral pelvic masses would be more consistent with PCOS whereas a unilateral pelvic mass may be more consistent with a neoplasia. Remember, too, that the pelvic exam may not reveal any masses in a patient with PCOS.

Laboratory Studies

The results of the history, in concert with the physical examination, will guide the laboratory work up (Table 1). This testing is designed to exclude life-threatening tumors and promote long-term health.

Endocrine screening. Prolactin and thyroid-stimulating hormone (TSH) levels are tested to rule out pituitary or thyroid disease as an etiology of anovulation. LH and follicle-stimulating hormone (FSH) may be analyzed, and they are usually seen in a ratio of > 2.5 to 3. However, a normal LH/FSH ratio does not exclude the diagnosis of PCOS. An FSH level will also help rule out premature ovarian failure in a woman with amenorrhea.[1,6,9,15]

Total testosterone and dehydroepiandrosterone sulfate (DHEAS) are evaluated to rule out an androgen-producing neoplasm. Total testosterone levels of 200 ng/dL are not generally seen in PCOS and suggest a virilizing tumor. DHEAS is a weak androgen that primarily comes from the adrenal glands. A level greater than 800 mcg/dL suggests a virilizing adrenal tumor.

17-hydroxyprogesterone (17OH-progesterone) is a useful screen for late-onset congenital adrenal hyperplasia (LOCAD). 17OH-progesterone levels less than 2 ng/mL are normal. A level > 5 ng/mL is diagnostic for LOCAD. A value between 2 ng/mL and 5 ng/mL should prompt an investigation with an adrenocorticotropic hormone stimulation test. If there is a suspicion for Cushing's syndrome, you may get a 24-hour urine for free cortisol or do a 1-mg dexamethasone suppression test overnight.

Cardiac risk profile. Because PCOS patients have hyperandrogenism, they are at an increased risk of cardiovascular disease. It is imperative, then, that the patients are screened for an abnormal HDL, cholesterol, and triglycerides at 35 years of age. Normal results should be repeated in 3-5 years. If these results are abnormal, these entities can be treated early, thus reducing the risk of cardiovascular disease.

Glucose testing. Glucose tolerance testing is important. As many as 35% to 45% of PCOS patients will have impaired glucose testing and about 7% to 10% will have type 2 diabetes mellitus. A fasting glucose to fasting insulin ratio less than 4.5 is predictive of insulin resistance. Values on the 2HR glucose tolerance test are as follows: 2H < 140 mg/dL (normal); 140-199 mg/dl (impaired glucose); and > 200 mg/dL (type 2 diabetes).[13,17]

Endometrial Aspiration

Many PCOS patients have unopposed estrogen stimulation for prolonged periods of time and are thus at risk for endometrial hyperplasia or endometrial carcinoma. Any PCOS patient with prolonged oligomenorrhea or amenorrhea or a patient with PCOS who is older than aged 35 years and has irregular bleeding should have endometrial aspiration to rule out endometrial carcinoma. An important point to remember is that advancing age is not a factor in deciding to obtain endometrial aspiration in patients with PCOS as it is in non-PCOS patients.

Radiologic Studies

An enlarged uterus or enlarged ovaries palpated on pelvic examination suggests a need for a pelvic ultrasound to distinguish uterine fibroids from an adnexal mass. If a patient has elevated DHEAS, adrenal imaging is indicated. An important caveat to remember is that polycystic ovaries can been seen in a number of healthy women who do not have PCOS, and women with PCOS do not always have radiographically demonstrated polycystic ovaries. Remember, by ultrasound, 25% of "normal" ovulating women would have polycystic-appearing ovaries.[5,6,9,18]

A transvaginal ultrasound should be done, as 90% of virilizing tumors can be identified with this method. Polycystic ovaries are also better evaluated transvaginally than transabdominally. Ovaries will have a typical appearance of enlarged subcapsular small follicles (> 10 mm) -- follicles are normally 2 mm to 10 mm in diameter. The ovarian volume in women with PCOS is > 10 cm^3 and the normal range is 4.7-5.2 cm^3.

Differential Diagnosis

Premature ovarian failure, rapid weight loss, extreme physical exertion, low body mass index (BMI) as in anorexia nervosa, and pregnancy will cause abnormal menstrual cycles (Table 2). Discontinuation of oral contraceptives may also cause amenorrhea. The latter is called post-pill amenorrhea. A pituitary adenoma, hyperthyroidism, or hypothyroidism will also cause a change in the menstrual cycle.

Other important etiologies to consider include congenital adrenal hyperplasia, late-onset adrenal hyperplasia, and Cushing's syndrome. Tumors of the adrenal gland or the ovaries may also present with menstrual irregularities.[8,9,16]

Treatment Options

Weight Loss

Women with a BMI of greater than 27 kg/m^2 are considered overweight, and they are often insulin resistant. Women with a BMI of > 30 kg/m^2 are considered obese and are almost always insulin resistant. Weight loss, even as a little as 5% to 7%, can decrease the amount of circulating androgens and, thus, will induce ovulation. Weight loss is also associated with decreased insulin and testosterone levels and an improved lipoprotein profile. These patients usually do the best when many members of a healthcare team, including a nutritionist, are actively involved in their care.[1,3,8]

Hormonal Treatments

Combination oral contraceptives (OCs) provide many benefits to the PCOS patient and have for a long time been the mainstay of treatment. The progesterone component of the OC provides protection for the endometrium from unopposed estrogen. Also, OCs suppress ovarian, adrenal, and peripheral androgen metabolism, which in turns reduces free

testosterone. OCs also suppress LH levels, which then decrease testosterone production by the ovaries. Similarly, OCs inhibit 5 alpha-reductase in the skin, which helps with acne. For those patients not wanting to become pregnant, OCs provide a reliable form of birth control in addition to providing a regular monthly menstrual cycle.

There are no studies that suggest that one OC is better than another for the treatment of PCOS. All OCs, whether they carry an FDA indication, are antiandrogenic. Once a patient has decided that she wants to try and conceive, she should then stop her OCs and promptly begin attempts to conceive. There is no need to wait the traditional 3 months before attempting a pregnancy. This is important because circulating androgens are at their lowest point immediately following OC use, and these patients will more likely ovulate at that time and not require an ovulation induction drug.[1,9,19]

Progestins work well in the patient who is not a candidate for OCs due to smoking, hypertension, or other contraindications. The progestin will protect the endometrium from chronic exposure to estrogen. The progestins, however, will not protect against a pregnancy.[6,9]

Insulin-Sensitizing Agents

Metformin (*Glucophage*) and troglitazone (*Rezulin*) are 2 insulin-sensitizing agents that have been shown to be successful in treating anovulation in the infertile PCOS patient. However, because of reports of severe liver toxicity, troglitazone was removed from the market, so metformin is now the insulin-sensitizing agent of choice. The newer agents on the market, rosiglitazone (*Avandia*) and pioglitazone (*Actos*), have not been extensively studied.

Insulin-sensitizing agents are indicated in patients with type 2 diabetes mellitus, elevated fasting insulin levels, or elevated 2-hour value on the glucose tolerance test. Metformin 1500-2000 mg per day in 2 to 3 divided doses is prescribed to stimulate resumption of normal menses and ovulation. Generally, it takes about 2 to 4 months for results. Prior to starting metformin, serum creatinine levels should be evaluated. Levels less than 1.4 mg/dL are necessary to reduce the rare complication of lactic acidosis.[1,3,8]

Since few studies report the use of insulin-sensitizing agents in PCOS patients who do not have insulin resistance, their use is not indicated. However, in time, these agents may be used to treat all patients with PCOS.[1,3,8]

Fertility Therapy

Clomiphene (*Clomid*) may be prescribed for PCOS patients who are anovulatory and desire pregnancy. Once the patient has conceived, clomiphene should be discontinued. If the patient was taking metformin, it should also be discontinued, as it is not FDA approved for use during pregnancy.[1,3,8]

Treatment of Hirsutism

There are many antiandrogenic agents that work well to reduce hirsutism. Oral contraceptives work well because they increase SHBG, which results in lower levels of active androgens. Also, the progestin component in the OCs inhibit 5 alpha reductase in the skin, which helps decrease the amount of hirsutism.

Spironolactone is an aldosterone antagonist that works well to control hirsutism by interfering with androgen synthesis. The recommended dose of spironolactone is 100-200 mg/day in 2 divided doses. There are few side effects associated with this drug. However, because it is a potassium-sparing diuretic, be aware of the potential for hyperkalemia with prolonged use. Flutamide (*Eulexin*) and finasteride (*Proscar*) are other antiandrogenic drugs. They are costly and have many side effects, thus making them less appealing options. The length of the hair cycle is long, so the response of these drugs should not be expected for at least 3-6 months. This is an important point to stress to the patient.

Nonpharmacologic treatments for hirsutism may include bleaching, wax stripping, shaving, or the use of hair removal creams or electrolysis. Despite popular beliefs, these approaches do not accelerate the rate of hair growth.[1,9]

Surgical Treatment

Ovarian wedge resection is a surgical procedure that was once done for patients with PCOS. In this procedure, a portion of the ovary was removed and the remainder of the ovary was sutured back together. This caused a reduction in LH secretion and androgen production. However, due the severe adhesive disease that ensued, this procedure has all but been abandoned. Ovarian drilling may sometimes be used because there is much less adhesion formation following this procedure. Ovarian drilling is another surgical procedure that involves cauterizing the small follicles on the surface of the

ovary. By cauterizing these follicles, androgen production will be decreased.[9]

Case Presentation

Barbara is a 25-year-old morbidly obese African American female, gravida 0, who presented to the gynecology office for evaluation of irregular menses since menarche. The patient stated that on average, she has 1 period every 6 months. When she does have her period, she bleeds very heavily, passing large clots, and has a lot of cramping. She also complained about excessive facial hair, which requires her to shave at least once every several days, and a lot of hair on her abdomen and arms. Barbara stated that her mother also has a lot of facial hair but doesn't think that she does anything about it.

She denied any change in her voice or increase in the size of her muscles. She has been morbidly obese since she was a young teenager. She denied any headaches, blurred vision, or discharge from her nipples. She also denied any hyper/ hypothyroid symptoms. She has never had any surgery and has never conceived, despite several years of trying. Barbara is not currently taking any medication and has never used any form of contraception.

On examination, she was clearly hirsute (Ferriman-Gallowey score of 10), especially in the chin and midabdominal regions. Her BMI was 32. Her pelvic exam was unremarkable, including no evidence for clitoromegaly, but her uterus and adnexa were very difficult to assess secondary to the patient's morbid obesity. The rest of her physical exam was unremarkable. Because she had been amenorrheic for 6 months, an endometrial aspiration was performed. The uterus sounded to 8 cm and there was a good amount of tissue on return.

A uterine ultrasound was performed, which revealed a normal appearing uterus, with an endometrial stripe of 6 mm and bilateral normal ovaries. Specifically, there was no evidence for polycystic ovaries.

Laboratory studies were undertaken to further evaluate her problem. Her FSH was normal, but her LH was elevated. Her TSH, prolactin, chemistry panel, cholesterol, triglycerides, HDL, and low-density lipoprotein (LDL) were all within normal limits. Her fasting insulin level was elevated at 36 UU/mL; fasting blood sugar was 130 mg/dL, and the 2-hour value on glucose tolerance test was 233 mg/dL. Her total testosterone was 78 ng/dL, and her free testosterone was 30 pg/mL (normal range, 1-21 pg/mL.) Her 17OH-progesterone was normal at 92 ng/dL, as was the DHEAS at 131 ug/dL. The endometrial aspirate showed proliferative endometrium without hyperplasia or neoplasia.

The clinical and laboratory results were consistent with PCOS. Because she desired a pregnancy, she was a candidate for metformin not only for control of her blood sugar but also to help regulate her menstrual cycles. She also required clomiphene to induce ovulation. After being started on a diet, an exercise program for weight loss, and metformin, her blood sugars responded well. After 6 months of blood glucose control, menstrual regularity, and increasing doses of clomiphene, she became pregnant. Today, Barbara is doing well in our high-risk OB practice.

Conclusion

PCOS is much more than just oligomenorrhea, amenorrhea, or infertility. PCOS encompasses many long-term health problems such as the development of cardiovascular disease, type2 diabetes mellitus, and prolonged exposure to unopposed estrogen, which can lead to endometrial hyperplasia and endometrial carcinoma. Clinicians need to be aware of the risk factors for PCOS and intervene with a preventive approach, which may restore normal menstrual function, ovulation, and fertility for those desiring it. We can also prevent or limit the complications from which PCOS patients suffer, such as cardiovascular disease, diabetes mellitus, and increased risk for unopposed estrogen.

Disclosure

Mac Pannill, MPAS, PA-C, has no significant financial interests to disclose.

Tables

Table 1. Laboratory Studies

LH

FSH
TSH
Prolactin
Lipid panel (cholesterol, HDL, LDL, and triglycerides)
Fasting insulin level
2-hour 75-g glucose tolerance test
DHEAS
Testosterone
Free testosterone
17-Hydroxyprogesterone

LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DHEAS, dehydroepiandrosterone sulfate

Table 2. Differential Diagnoses in Polycystic Ovaries

Pregnancy
Premature ovarian failure
Hyperthyroidism
Hypothyroidism
Pituitary adenoma
Late-onset congenital adrenal hyperplasia
Congenital adrenal hyperplasia
Androgen-producing tumor of the ovary or adrenal gland
Discontinuation of oral contraceptives
Rapid weight loss
Extreme physical exertion

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