Polycystic Ovary (Stein-Leventhal) Syndrome: Etiology, Complications, and Treatment

KARRI LYNN HOYT, MARGARET C SCHMIDT

Polycystic ovary syndrome (PCOS) occurs in approximately 3% to 5% of the female population and may be the leading cause of infertility in those of reproductive age. PCOS presents clinically with a variety of signs and symptoms; the most common being menstrual irregularities, hyperandrogenism, infertility, and obesity. The true pathophysiology has not been clearly elucidated; however, there is growing agreement that gonadotropin dynamic dysfunction, hyperandrogenism, and insulin resistance are key features. The diagnosing of PCOS involves radiologic and laboratory studies. Radiologic studies typically include pelvic ultrasound; laboratory data should be obtained regarding pertinent gonadotropins and other hormone levels. PCOS is not a benign condition. It may lead to complications involving glucose metabolism, dyslipidemias, cardiovascular disease, and cancer. The goals of treatment should focus on restoring menstrual regularity, decreasing androgen excesses, and decreasing insulin resistance.

ABBREVIATIONS: AN = acanthosis nigricans; FSH = follicle stimulating hormone; GnRH = gonadotropin releasing hormone; HAIRAN = hyperandrogenic-insulin resistance-acanthosis nigricans; hCG = human chorionic gonadotropin; HDL = high-density lipoproteins; LDL = low-density lipoprotein; LH = luteinizing hormone; OCP = oral contraceptive pill; PCOS = polycystic ovary syndrome; SHBG = sex hormone binding globulin; TSH = thyroid stimulating hormone.

INDEX TERMS: amenorrhea; follicle stimulating hormone; hyperandrogenism; infertility; luteinizing hormone; polycystic.

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CASE STUDY

A 27-year-old female presents to her primary care provider with complaints of amenorrhea times 11 months. Patient's past medical history is significant for starting menses at age 14. Menses have never been regular and when they do occur they are light. The longest time without a menstrual cycle is 18 months. A prior provider initiated progesterone withdrawal as a treatment; however, patient only used treatment once. Patient indicates that she is not pregnant at this time. Family history is significant for a sister and several paternal cousins with menstrual irregularities.

On physical exam the patient is of normal weight for height; it is noted that patient has slightly darker hair above the upper lip, small breasts with sparse hair around the areola, hair in the midline below the umbilicus, and hair on the inner thigh. It is also noted that patient has acne scarring and active pustules on back, upper chest, and shoulders.

Laboratory data are collected including follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, human chorionic gonadotropin (hCG), prolactin, glucose, and insulin levels. Results indicate an LH:FSH ratio of >6, testosterone >50 mg/dL; negative hCG, and prolactin, glucose, and insulin levels within normal reference range.

Radiologic studies (abdominal ultrasound) reveal bilateral cystic ovaries; however the ovaries do not appear to be significantly enlarged.

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders seen in women of reproductive

age.[1,2] It may also be the most common cause of infertility for the same age group.[1,3] The classic picture of PCOS was first described by Stein and Leventhal in 1935.[4] They reported on seven women who had the associated characteristics of amenorrhea, hyperandrogenism, and obesity in association with bilaterally enlarged polycystic ovaries. Six of the seven women had menstrual irregularity that began in early menarche progressing to amenorrhea; five of the seven were infertile. Laparotomy revealed ovaries with thickened tunica and multiple cysts. Resection of half to three-fourths of the ovaries resulted in normal menstrual function for all of the women. Stein and Leventhal concluded that the crowding of the cortex led to the observed symptoms. Increases in our understanding of this syndrome have disproved this theory. Instead, it is now accepted that there are multiple hormonal factors that contribute to the symptoms of PCOS and the clinical presentation is much more variable including amenorrheic women who appear otherwise healthy. However, the description given by Stein and Leventhal remains the basis for defining the syndrome.

Data on prevalence is inconsistent, owing to the lack of well-accepted criteria for diagnosis. The incidence of PCOS is reported to be 3% to 6% of the female population on average with a range as high as 21% to 22% in a study of Pima Indians.[2,5] Studies using the criteria of oligomenorrhea and hyperandrogenism report a slightly lower frequency of occurrence in black females (3.4%) as opposed to white females (4.6%).[2] The disease has no predilection for race, although the presenting signs and symptoms may differ with ethnicity. The best estimate of prevalence may come from a population-based study by Knochenhauer.[6] These researchers assessed 277 women undergoing routine pre-employment physical exams using the criteria of menstrual cycle characteristics and clinical androgen excess. The serum androgen levels were measured in 198 of the women who were not using hormonal therapy and PCOS prevalence was estimated to fall within the range of 3.5% to 11.2%.

CLINICAL PRESENTATION

PCOS may present with a wide variety of signs and symptoms (Table 1). The most common clinical presentations include menstrual irregularities, symptoms of hyperandrogenism, infertility, and obesity. Menstrual irregularities range from oligomenorrhea to amenorrhea.[5] Women affected with PCOS usually begin menarche at a normal age (10 to 16 years of age), but their cycles remain irregular generally progressing to amenorrhea.[1] In a review reported by Goldzieher and Axelrod, amenorrhea was reported in 47% of patients.[7] Hunter reports a study where 70% of women with PCOS reported menstrual irregularities.[1] However, there is a small percentage of women affected by PCOS who report regular menstrual cycles.

Signs of androgen excess include course hair growth in androgen-dependent areas of the body (sideburns, chin, upper lip, peri-areola, chest, lower abdominal midline and thigh), as well as truncal obesity, and acne.[1,7] These signs may range from mild to moderate with approximately 70% of women reporting some form of hirsutism. Signs of virilization, though rare, may occur, including clitormegaly, voice changes, increased muscle mass, and temporal baldness.[1]

Obesity is another complicating factor of PCOS, but an explanation for the high prevalence of obesity among women with PCOS is unknown. It is generally seen as a central or truncal accumulation of adipose tissue and is evidenced by an increased hip-to-waist ratio (>0.8).[9] Obesity may also contribute to menstrual irregularities/infertility and androgen excess as these conditions have been shown to improve

Table 1. Possible presenting symptoms of polycystic ovary syndrome

Frequent
Hirsutism
Infertility
Obesity
Oligomenorrhea
Common
Acanthosis nigricans (indicative of hyperinsulinemia)
Acne
Alopecia
Amenorrhea
Impaired glucose tolerance
Seborrhea
Rare
Acral hypertrophy
Endometrial carcinoma
Hypertension
Non-androgen secreting ovarian tumors, i.e., dermoid cyst
True virulization

Adapted from: [2,8]

with weight loss.[2] Obese women with PCOS appear to have a higher prevalence of hirsutism than women of normal weight with PCOS:70% to 73% vs. 56% to 58% respectively.[7] Menstrual irregularities were also more prevalent in obese women than non-obese:78% to 88% vs. 68% to 72% respectively.[7] Women who do have hyperandrogenism along with obesity are at greater risk for dyslipidemia, i.e., increased triglycerides and low-density lipoproteins (LDL), and decreased high-density lipoproteins (HDL).[5] It is important to remember however, that obesity does not necessarily have to be present for dyslipidemia to be present.

Acanthosis nigricans (AN), described as velvety, raised, pigmented skin typically found on the posterior neck, axillae, and within the mammary folds, is a skin condition often associated with PCOS. AN is evident in 1% to 3% of women with PCOS and more commonly found in those who are obese.[7] An investigation for AN should be part of any physical exam for a patient with suspected PCOS. If found, AN should additionally alert the practitioner to the possibility of diabetes, hypertension, hyperlipidemia, and cancer.[10] The symptom group of hirsutism, AN, and insulin resistance is known as the HAIRAN (hyperandrogenic-insulin resistance-acanthosis nigricans) syndrome and is likely a more severe form of PCOS.[7,10]

The classic descriptors of amenorrhea, hirsutism, infertility, and obesity do not all have to be present for the diagnosis of PCOS. Because there is a lack of agreement as to what actually constitutes PCOS, the definition from the 1990 National Institutes of Health/National Institute of Child Health and Human Development conference may be useful in determining if a patient has PCOS.[11] This definition proposes the following criteria: a patient must have ovulatory dysfunction and evidence of clinical and laboratory substantiated hyperandrogenism without the presence of other causes of hyperandrogenism.

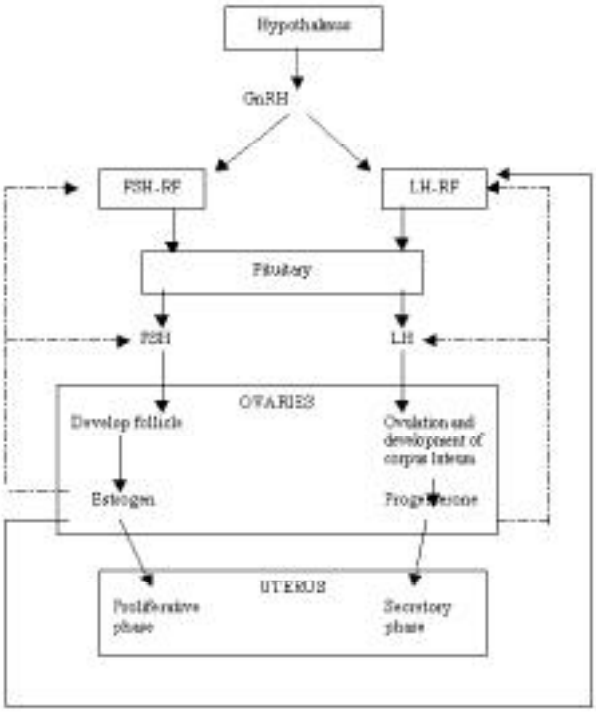
Hyperandrogenism may be a sequelae of a number of other medical conditions. The most serious of these include androgen producing tumors, hyperthecosis (hyperplasia of the theca interna, a basic component of the preovulatory follicle responsible for androgen substrate), adrenal hyperplasia, and tumors of the adrenal glands. These diagnoses should be ruled out as the cause for hyperandrogenism before conferring the diagnosis of PCOS.

Other disease states may contribute to ovulatory dysfunction including hypothyroidism, and hyperprolactinemia. Anovulation may be associated with rapid weight loss, extreme physical exertion, eating disorders, and certain medications. Each of these conditions appears to affect the levels of follicle stimulating hormone (FSH) and/or luteinizing hormone (LH) in some way.[1]

PATHOPHYSIOLOGY

The female hormonal cycle depends on the intricate interactions between hypothalamic gonadotropin-releasing hormone (GnRH), the pituitary gonadotropins LH and FSH, and the ovarian steroid hormones estradiol and progesterone. During a normal cycle, FSH release stimulates the growth of the follicle, which in turn produces estrogens (Figure 1). The rising level of estrogens facilitates the release of LH, which in turn stimulates the release of the ovum from

Figure 1. Female hormonal cycle



——— stimulates
-------- inhibits

GnRH: gondaotropin releasing hormone
FSH-RF: follicular stimulating hormone releasing factor
LH-RF: lutenizing hormone releasing factor
FSH: follicular stimulating hormone
LH: lutenizing hormone

the follicle (ovulation), and the production of progesterone. If fertilization/implantation does not occur, the level of progesterone begins to fall causing menses to occur and the level of FSH to rise, thus renewing the cycle. FSH also functions as a stimulator for the enzyme aromatase within the ovarian granulosa cells that convert androgens to estradiol. LH plays a role in the conversion of cholesterol to androgens via the P450c-17 system.[10,12] If any of the hormones becomes chronically elevated or suppressed, dysfunction of the entire cycle may occur.

While the true etiology or defect that leads to PCOS remains unknown, many of the contributing factors form a perpetuating cycle. Possible pathways for the origin of PCOS include: disordered signaling of the hypothalamic-pituitary axis for release of gonadotropins; problems with hormone receptors on the follicles; altered steroid production; disorder of paracrine or autocrine regulation; or the effect of insulin and insulin resistance.[10] Although none of these pathways has been definitively proven, there is growing agreement that the key features of gonadotropin dynamic dysfunction, hyperandrogenism, and insulin resistance are linked to a cause.[1,12]

Gonadotropin dysfunction feeds into the pathophysiology of PCOS. In contrast to the fluctuation of hormone levels in a normal cycle, those with PCOS appear to reach a 'steady state' for levels of LH and FSH in the body.[13] In particular, there appears to be a much higher level of LH, in general and in relation to the FSH level. This 'steady state' negates the effect of the LH surge needed for the lutenization of the follicle. The resulting condition includes sustained annovulation and increased levels of androgens. FSH levels are generally considered to be within normal reference ranges, but they too lack the cycle variation necessary for regulated follicular development.[7] Although the ovaries are not secreting an increased level of estrogen, there appears to be an increased level in the circulation. This increase may be due to the peripheral conversion of androstenedione to estrone.[13] This higher level of estrogen stimulates the continued release of LH. Elevated estrogen levels suppress FSH release via impact on the pituitary.

Normal ovarian function relies on the interplay between LH-stimulated theca cells and FSH stimulated granulosa cells for the coordinated production of both androgens and estrogens. Androgens appear to be a 'necessary evil' for normal ovarian function.[12] They are needed for the production of estradiol by the granulosa cells. In excess, androgens interfere with the maturation of the follicles and prevent the emergence of a dominant follicle. In PCOS, androgen excess is reflected in the higher circulating levels of testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogestrone (17-OHP), and estrone.[13] Higher circulating levels of these androgens may be associated with several of the more common presenting symptoms of PCOS. The level of sex hormone binding globulin (SHBG) is influenced by the circulating levels of testosterone (inhibitory) and estrogen (stimulatory). Higher levels of testosterone cause SHBG production to decrease. The consequence is increased levels of free circulating estradiol considered to be a predisposing factor to the development of endometrial and breast cancers.[7] Free estradiol levels may also correspond to increased levels of estrogen in the feedback loop for the stimulation of LH.

Insulin has recently been recognized as a factor in ovarian hyperandrogenism. Generally, hyperinsulinemia is regarded as a lack of cellular insulin sensitivity with respect to glucose metabolism, and occurs more frequently in those who are obese. Hyperinsulinemia occurs to some degree in most women with PCOS; Dunaif reported that hyperinsulinemia occurred in obese and non-obese women with PCOS.[14] While some somatic cells may be insensitive to insulin's action, the ovaries remain sensitive, and produce more androgens.[7] High insulin levels also reduce synthesis of SHBG by the liver, creating a relative surplus of free sex hormones (androgens and estrogens). It is unclear why women with PCOS have insulin resistance.

In summary, the pathogenesis of PCOS appears to involve the following: 1) excess androgens are converted to estrogens by peripheral adipose tissue; 2) increased circulating levels of estrogen stimulate the secretion of LH while inhibiting the secretion of FSH; and 3) the increased levels of LH stimulate the theca cells of the ovary to produce higher levels of androgens.[15]

DIAGNOSTIC STUDIES

Controversy exists over what studies—laboratory and/or radiographic—should be employed to identify PCOS. Many women with PCOS have elevated serum levels of LH, testosterone, androstenedione, estradiol, estrone, prolactin (>30%), fasting insulin, an increased LH:FSH ratio, and decreased SHBG.[16] Additionally, multiple cysts may be evident on the ovaries.[1] The level of FSH may be within reference limits or decreased.

The levels of FSH and LH are commonly used to diagnose PCOS as these hormones are directly involved in the pathogenesis of this disorder. LH and FSH are synthesized and released from gonadotropin cells in the anterior pituitary in response to increased levels of GnRH. It is important to note that the release of both LH and FSH is pulsatile and LH displays a circadian rhythm.[17] The amount of these hormones in circulation at any given time is dependent upon the day of the menstrual cycle (Figure 2). Therefore, single blood test sample results must be carefully interpreted based on reference intervals correlated to the phase of the patient's menstrual cycle during which the sample was obtained (Table 2). An elevated LH:FSH ratio is considered by some to be diagnostic for PCOS.[1] There is no consensus as to how high the ratio must be. Sources generally report values of LH:FSH greater than 1.5 to 3.0 as indicative of PCOS.[17,18] A ratio of LH:FSH of greater than three is considered diagnostic for the disorder by many researchers.[1] Although cross-reactivity among the similar structures of LH, FSH, TSH, and hCG contributed to erroneous radioimmunoassay results in the past, current assays are capable of measuring any one hormone in the presence of the others.[17,19] This specificity enhances the use of these tests in evaluating a patient for PCOS. Prolactin may be increased in >30% of women with amenorrhea. A prolactin level >20 ng/mL should be re-checked in conjunction with thyroid stimulating hormone (TSH) to rule out the possibility of a thyrotropin mediated increased prolactin.[16]

Table 2. Serum immunochemiluminometric assay (ICMA) reference intervals for luteinizing hormone, follicle stimulating hormone, and progesterone

Cycle stage	LH* (mIU/mL)	FSH† (mIU/mL)	Progesterone (ng/mL)
Follicular	1.6 – 1.3	3.4 – 10	<0.09 – 1.5
Mid-cycle	15 – 62	5.7 – 20	
Luteal	<0.7 – 8.1	1.9 – 10	2.3 – 25
Mid-luteal	3.5 – 25		
Post-menopausal	>14	41 – 124	<0.09 – 0.7
Oral contraceptives	<0.7 – 8.0	<4.9	<0.09 – 0.4
ERT‡		9.7 – 111	
Pre-puberty		0.5 – 3.7	
Pregnancy			
1st trimester			8.1 – 42
2nd trimester			15.2 – 130
3rd trimester			49.1 – 227

* LH = luteinizing hormone
† FSH = follicle stimulating hormone
‡ ERT = estrogen replacement therapy
Adapted from the Duke University laboratory manual, Duke University Medical Center

Additional hormones important in the diagnosis of PCOS include measuring the androgens, which are thought to contribute to the perpetuating cycle that is this syndrome. Although some debate exists, employing serum levels of testosterone and other androgens in the diagnosis of PCOS is recommended, as some women with PCOS have no overt clinical signs of androgen excess. Suggested laboratory and radiographic studies are listed in Table 2.

The use of ultrasound findings as a means of diagnosis for PCOS is debatable.[7] Classical presentation of ovaries seen on ultrasound include 10 or more cysts per ovary, each cyst measuring 2 to 18 mm, and arranged in a 'pearl necklace' pattern on the periphery of the ovary. The ovarian stroma is thickened and the volume increased. The number of cysts is the most reproducible parameter used in describing the ovaries of PCOS.[7] Several studies have looked at the correlation between ultrasound findings and the diagnosis of PCOS. Fox compared women with normal ovaries on ultrasound with women who had hirsutism and oligomenorrhea.[20] They found that 14% of the oligomenorrhic women fit a clinical and/or biochemical diagnosis for PCOS, but on ultrasound lacked the increased number of cysts. Another researcher compared transvaginal ultrasound findings among subjects who had clinical PCOS to findings in normal control subjects.[21] It was found that approximately 50% of the PCOS subjects had <10 cysts per ovary and normal ovarian volume. Hence, the diagnosis of PCOS cannot hinge upon ultrasound findings. Polycystic ovaries can be found in women who do not display any of the other clinical symptoms for PCOS. Several investigators have reported finding polycystic ovaries in 6% to 22% of a normal population.[22] Ultrasound may display an association

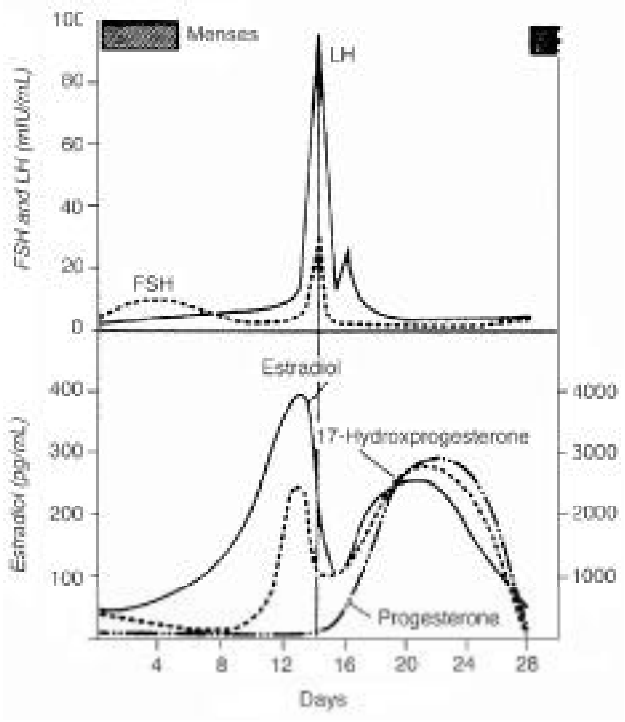
with the clinical findings of PCOS, but is not necessary for the diagnosis of PCOS.

COMPLICATIONS

The dysfunction of multiple hormonal systems that characterize PCOS may place a woman at increased risk for a number of other diseases including dysfunctional glucose metabolism, dyslipidemia, cardiovascular disease, and cancer of the endometrium, ovary, and breast. There is some controversy regarding the data for an increased incidence of hypertension.[2,5]

Dunaif found higher insulin levels and greater glucose intolerance in women with PCOS regardless of weight status when compared to normal control subjects.[2,5,14] The rate of glucose intolerance and diabetes type 2 is substantially higher in women with PCOS than in normally cycling control subjects. A study including a group of women 14 to 44 years of age found a 31% prevalence of glucose intolerance and a 7% incidence of type 2 diabetes.[25] The Nurses' Health Study, conducted by Harvard's School of Public Health on women of reproductive age, demonstrated prospectively that those women who have oligomenorrhea also have a significant increase in the risk of developing type 2 diabetes.

Figure 2. Relationship of hormone levels and day of menstrual cycle



Dyslipidemia is well noted in women with PCOS. Lipid levels are significantly elevated above the normal ranges for triglycerides and low-density lipoproteins (LDL), with decreased levels for high-density lipoproteins (HDL).[2,5] These abnormalities appear to persist even when data are corrected for the higher body mass index associated with PCOS.[2] One source hypothesizes an association with hyperlipidemia and the hyperandrogenistic state of PCOS.[5]

PCOS carries a known risk for cardiovascular disease. The risk varies with the levels of LDL, HDL, triglycerides, and total cholesterol. Increases in LDL, triglycerides, and total cholesterol levels, and a decreased level of HDL increase the risk of acquiring heart disease. Reports have been published stating that women with type 2 diabetes have a threefold greater risk of cardiovascular disease and a twofold greater risk related to hypertension.[24,25] Atherosclerosis has been reported to occur at higher rates in women with PCOS. A study of 143 women, 60 years of age and younger, reported a significantly greater and more extensive coronary atherosclerosis (defined as >50% stenosis) in those with PCOS (42%) than those without.[2] However, Pierpont and colleagues conducted a long-term follow-up for mortality in women with PCOS related to cardiovascular disease and re-

Table 3. Suggested laboratory and radiographic studies for the diagnosis of PCOS

Endocrinology:
Testosterone level
Luteinizing hormone level
Follicle-stimulating hormone level
DHEA-sulfate level
17-hydroxyprogesterone level
Prolactin level
Urinary:
Human chorionic gonadatropin level
Other tests:
Lipid profile (total cholesterol, LDL*, HDL†, triglycerides)
Oral glucose tolerance test
Pelvic ultrasound
Dexamethasone suppression test

* LDL = low-density lipoprotein
† HDL = high-density lipoprotein
Adapted from[2]

ported no increase in the ratio of observed-to-expected deaths from all circulatory diseases.[21] They raise the question of prolonged unopposed estrogen exposure in PCOS and whether it is protective against cardiovascular disease related outcomes, which has yet to be definitively answered.

Several researchers have reported on the risk of malignancies of the endometrium, breast, and ovaries in women with PCOS.[1,2] The risk appears to be greatest for endometrial cancer. The effects of exposure to unopposed estrogen over an extended period of time may place a woman at risk for endometrial hyperplasia or cancer, and possibly breast cancer. The risk of endometrial cancer has been reported as two to threefold greater in women with PCOS than in normal cycling control subjects.[1,2] A linkage of hyperinsulinemia to endometrial carcinoma was suggested.[2] A study of 97 young women with endometrial hyperplasia reported a 25% prevalence of PCOS.[27] Since endometrial hyperplasia is often a precursor to endometrial cancer, a relationship between PCOS and endometrial cancer could be suggested.

The risk of breast cancer with PCOS is controversial. Several small observational studies suggest that chronic anovulation during the reproductive years may raise the risk for the development of cancer by three to four fold during the postmenopausal period.[1,2] This association was not seen in the premenopausal period.[2] It is known that early menarche and late menopause are predictors for breast cancer and as such, the anovulatory state of PCOS may be protective.[2] However, there is also evidence that with PCOS there are long periods of direct estrogen exposure, considered a link to an increased risk of breast cancer.

An association with ovarian cancer and PCOS has also been hypothesized. The Cancer and Steroid Hormone study reported women with ovarian cancer were more likely to report a prior diagnosis with PCOS than control subjects even after adjusting for age, parity, oral contraceptive pill (OCP) use, history of infertility, and education.[28] It has been noted that longitudinal data does not support the association between PCOS and ovarian cancer, and that further studies are needed to clarify any association.

TREATMENT

Treatment for PCOS is focused on decreasing or ameliorating the symptoms as opposed to effecting a cure. Treatment modalities rarely improve all aspects of the disease. The protocols attempt to decrease insulin resistance, and the effect of hyperandrogenism, thereby normalizing the menstrual cycles, and re-establishing ovulation. The desire for fertility may limit the use of certain therapies.

One of the simplest forms of treatment may be behavior modification. Recommendations for proper diet, regular exercise, and weight loss, if needed, apply to all women with PCOS.[1,29] Weight loss can effectively reduce the peripheral adipose stores, which may decrease the peripheral conversion of androgens to estrones. This reduction in available estrogens may reduce endometrial hyperplasia and restore ovulation. A reduction in androgens may also help to improve dyslipidemia. Behavioral modifications, therefore, are considered important to PCOS management, whether or not pharmacologic therapy is applied.

One of the most common treatment methods for PCOS is the administration of OCP, especially in those avoiding pregnancy.[10,30] OCPs depress production of androgens by the ovaries thus decreasing the effects of androgen excess. The outcome decreases aromatization of androgen to estrogen thus decreasing the estrogen pool. This effect stabilizes the endometrial lining and prevents onset of hyperplastic changes. Contraception is an additional benefit of the OCP treatment. OCPs will not reduce the hyperinsulinemic state often observed with PCOS.

In those who do not desire to conceive and/or are not at risk for being pregnant, the administration of progesterone in the form of medoxyprogesterone acetate may be applied on a monthly basis.[1,29] Progesterone will help decrease endometrial hyperplasia but will not decrease the level of ovarian androgens produced.[1]

Hyperinsulinemia was described as a hallmark for PCOS in 1981.[31] However, investigation into the use of anti-hyperglycemic drugs in the treatment of PCOS did not occur for almost 15 years thereafter. Metformin (glucophage) is the best studied of the insulin-lowering drugs. Valazquez studied it first in 1994.[32] The study involved 26 obese females who were placed on metformin for eight weeks. They reported a reduction in serum insulin levels as well as a 52% reduction in free testosterone. Studies have documented that lowering of insulin levels through the use of insulin-lowering drugs may ameliorate many of the abnormalities associated with PCOS including hyperandrogenism, irregular menstrual cycles, and ovulation irregularities, and potentially may effect a decrease in cardiovascular disease risk.
To date, approximately 10 authors have reported the benefi-

cial effects of metformin in treating PCOS.[33-41] The most recent study to demonstrate the long-term effectiveness of metformin treatment in obese women is by Moghetti, who used placebo and metformin in a group of 32 women.[41] They found that the group receiving the insulin-lowering drug had significant improvement in the regularity of the menstrual cycle and ovulation, as well as a decrease in serum androgen and LH levels. These findings were maintained throughout a one-year monitored period. Although most studies have focused on obese women, Nestler and Jakubowicz administered metformin to lean PCOS women and established similar declines in hormonal abnormalities and the attending sequelae as those found in the obese subjects.[33]

Not all investigations of metformin have noted beneficial effects in the treatment of PCOS. Several studies noted no beneficial effect.[42-45] Others involved morbidly obese subjects and the lack of effect may reflect the inability of the metformin to overcome the overwhelming androgen levels and hyperinsulinemia associated with morbid obesity regardless of PCOS status.

CONCLUSION

Polycystic ovary syndrome affects approximately 3% to 5% of the female population of reproductive age.[2,5] It is the number one cause of infertility in women of the same age group. There have been many advances in our knowledge of the multi-factorial causes of PCOS and in our ability to treat the symptoms of the disease. However, because this syndrome presages health risks not limited to infertility, but extended to the cardiovascular system and cancer of reproductive organs, clinicians need to be alert to the potential existence, signs, and symptoms of PCOS in female patients of all age groups. Work to develop more specific laboratory and/or radiologic diagnostic markers for PCOS is needed.

This paper was written while Karri Lynn Hoyt was a student in the Duke University Physician Assistant Program.

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