Polycystic Ovary Syndrome

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To the Faculty of Washington State University:

The members of the committee appointed to examine the ICNE Research requirements and manuscript of Anne D. Tweedy find it satisfactory and recommend that it be accepted.

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I wish to extend my sincerest appreciation to those who have helped to make my postgraduate experience a positive one. I have obtained such a solid base to the beginning of my career as I know my learning has only just begun. I have had such positive role models and teachers. Long distance learning wasn’t always easy, but I believe it was the best it could have possibly been. Without this opportunity, I wouldn’t be where I am today.

To Dr. Lorna Schumann: you have been a constant source of sound advice. I couldn’t have asked for a better advisor or chairperson. Thank you for the many questions you have answered and for always making yourself available to me. You have helped put my mind at ease on numerous occasions. You are a very gifted, wonderful teacher and clinician. I have been fortunate to have you touch my life.

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To my husband, Matthew, who is my constant source of strength and encouragement. It is because of you and your strong belief in me, that I am able to follow my dreams. With you, anything is possible.
POLYCYSTIC OVARY DISEASE

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ABSTRACT

Polycystic ovary syndrome (PCOS) is believed to affect up to 10% of women of reproductive age. It is a complex disorder that causes hyperandrogenemia and hyperinsulinemia resulting in infertility, irregular menses, acne, and hirsutism. Women with PCOS also have an increased risk for developing non-insulin dependent diabetes mellitus, dyslipidemia, ovarian cancer, and premature cardiovascular disease. The examiner should focus on the menstrual and reproductive history. The physical examination should focus on hair and acne distribution, presence of central obesity, and ovarian enlargement. The patient may or may not have polycystic ovaries as diagnosed on ultrasound. The diagnosis of PCOS is determined by a combination of ultrasonography, hirsutism, or hyperandrogenemia. The treatment of PCOS is based on symptomatic measures to treat hirsutism, obesity, irregular menses, and infertility. There is no cure for PCOS at this time.
TABLE OF CONTENTS

ACKNOWLEDGMENTS.............................................................................................. iii
ABSTRACT............................................................................................................. iv
LIST OF TABLES................................................................................................... vi
MANUSCRIPT
  BIBLIOGRAPHY................................................................................................. 14
  TABLES................................................................................................................ 18
  FIGURES............................................................................................................ 21
LIST OF TABLES

1. Clinical Presentation of PCOS................................................................. 18
2. Algorithm/Pathway of Polycystic Ovary Syndrome............................... 19
3. Laboratory Test Price Ranges................................................................. 20
4. Polycystic Ovary Ultrasound................................................................. 21
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Introduction

Polycystic ovary syndrome (PCOS), once known as Stein-Leventhal syndrome, is believed to be a complex endocrine disorder of hypothalamic-pituitary dysfunction. It is typically characterized by excess serum androgen levels, impaired glucose tolerance, hirsutism, long-term anovulation, and infertility. It is believed to be the most common endocrine disorder in women of reproductive age (Franks, 1998). Polycystic ovary syndrome is the most frequent cause of anovulation and hirsutism and, in recent years, has been linked with a metabolic disturbance of a resistance to insulin (Franks, 1995).

Etiology/Prevalence

It is estimated that PCOS affects up to 10% of women of reproductive age, and, of those, 35% are affected with impaired glucose tolerance (Ehrmann et al., 1999). Polycystic ovary syndrome occurs in approximately 75% of cases of anovulatory infertility and over 80% of patients with hirsutism (Franks, 1998). In addition to reproductive dysfunction, women with PCOS have an increased risk for developing non-insulin dependent diabetes mellitus (NIDDM), dyslipidemia, and premature cardiovascular disease (Ehrmann et al., 1999; Franks, 1998). It is estimated that 625,000 new cases of PCOS are diagnosed each year (Ehrmann et al., 1999).

The exact etiology of PCOS is unknown, but there is evidence of autosomal transmission related to strong familial clustering. It is hypothesized that a gene or series of genes causes the ovaries to have increased susceptibility to insulin stimulation of androgen secretion, while blocking follicular maturation (Hopkinson, Sattar, Fleming, & Greer, 1998).
Typically, PCOS is diagnosed during the teenage years, because of menstrual disturbances and/or hirsutism (Conway, 1996; Franks, 1998). It can occur throughout the reproductive years and in previously fertile women (Greene et al. 1996). Since the abnormalities associated with PCOS typically appear around the time of puberty, the disorder probably begins in childhood and may even originate during intrauterine development (Cresswell, Barker, Osmond, Egger, & Fraser, 1997). Because only 10% to 20% of women with PCOS are symptomatic, the diagnosis of PCOS should be explored in all patients presenting with amenorrhea, infertility, or hirsutism (Marantides, 1997).

Pathophysiology

Although the pathophysiology of PCOS is not completely understood, it appears to include a combination of abnormally high luteinizing hormone: follicle stimulating hormone (LH: FSH) ratio, hyperandrogenemia, theca cell hyperplasia, and hyperinsulinemia. The pathophysiology of PCOS is related to an imbalance of LH to FSH. Typically, the FSH levels are suppressed and the LH levels are elevated without a midcycle surge (Marantides, 1997). The resulting abnormally high LH:FSH ratio is a hallmark of this disorder. The elevated LH level stimulates the theca cell in small ovarian follicles to secrete excessive amounts of androstenedione and testosterone. This causes an excess number of small follicles to accumulate without the development of preovulatory follicles, resulting in anovulation and dysmenorrhea (Barbieri, 1997).

Testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) are the three main androgens. In women, 60% of the circulating testosterone comes from direct ovarian secretion and 40% comes from the peripheral conversion of
androstenedione. Testosterone is the strongest androgen of the three with 98% circulating in a bound state. Approximately, 65% is strongly bound to sex hormone-binding globulin (SHBG) and 33% is weakly bound to albumin. It is only the free testosterone and some of the albumin-bound testosterone that is able to enter the target cells to exhibit an effect (Fitzgerald, 1998). It is believed that the hypothalamic imbalance causes excessive LH which results in an ovarian overproduction of total and free testosterone and androstenedione (Goroll, May, & Mulley, 1995).

While the ovary is believed to be the principal site of this excess androgen production, some women with PCOS may have an adrenal contribution to the increased circulating androgens (Rodin, Thakkar, Taylor, & Clayton, 1994). Some of the androgen is converted to estrone in the adipose tissue, causing a hyperestrogenic state, which stimulates endometrial proliferation. This results in irregular episodes of bleeding, aberrant follicular development, anovulation, and continued ovarian androgen production (Goroll, May, & Mulley, 1995; Thorneycroft, 1994). Estradiol production is impaired and multiple cysts form on the ovaries over a period of months to years due to the cessation of follicular development (Marantides, 1997). The increased androgens continue to be converted to estrogens in the adipose tissue and aggravate an already hyperestrogenic state (Thorneycroft, 1994).

Usually, women with PCOS are obese. Increased obesity is associated with worsening symptoms, due to its association with higher testosterone levels (Conway, 1996). Women with PCOS who are obese have higher serum levels of testosterone, as well as an increased prevalence of hirsutism (Conway, 1996). Douchi et al. (1995) found that women with PCOS who have an increased upper-half body fat ratio had significantly
higher levels of testosterone and dehydroepiandrosterone sulfate (DHEAS) levels in comparison to those with lower-half body fat ratio. The researcher further stated that upper-half body type obesity has been found to be associated with glucose intolerance and hyperlipidemia.

Insulin resistance, and the resulting hyperinsulinemia, are also principal underlying defects in PCOS (Hopkinson, Sattar, Fleming, & Greer, 1998; Ehrmann et al., 1999). The pathogenesis of insulin resistance appears to be related to a post-receptor defect in the adipose cells, although insulin continues to have stimulatory effects on ovarian thecal androgen production. The combination of hyperinsulinemia, the elevation of LSH levels, and the ovaries’ enhanced sensitivity to insulin result in thecal hyperplasia, increased androgen secretion, and arrest of follicular development. These changes cause anovulation with menstrual disturbance. Hyperinsulinemia further elevates circulating, free testosterone levels by inhibiting the sex hormone binding globulin secreted in the liver (Hopkinson et al., 1998).

Women with PCOS and either impaired glucose tolerance (IGT) or non-insulin dependent diabetes mellitus (NIDDM) have significantly higher levels of free and total testosterone when compared to those with normal glucose tolerance (Ehrmann et al., 1999). It is unknown whether hyperandrogenemia contributes to the development of IGT, or if it represents insulin resistance. The majority of women with PCOS and NIDDM typically have a first-degree relative who has been diagnosed with NIDDM (Ehrmann et al., 1999). This may indicate that the glucose intolerance found in some patients with PCOS may have a genetic component which may also involve defects in insulin action and secretion in addition to insulin resistance.
History

A detailed menstrual history focusing on duration, frequency, regularity, and intensity of the flow is necessary. Determine if the menses has ever been regular. If the patient is in childbearing years, pregnancy should be ruled out. Anovulatory bleeding should be suspected when the irregularity of menstrual periods is followed by months of amenorrhea. Ascertain whether the patient is experiencing emotional stress, weight loss, increased exercise, or chronic illness that could precipitate irregular periods. Assess the patient’s reproductive history which should include the birth control method, number of pregnancies, miscarriages, or abortions. Assess for complaints of dyspareunia, postcoital bleeding, vaginal discharge, pelvic pain, fever, trauma, and intrauterine device (IUD) use.

Physical examination

The physical examination should begin with height, weight, and vital signs. A pelvic and general physical exam should be done with focus on the degree and distribution of hair, the presence of secondary sex characteristics, and breast and genital atrophy. It is also important to observe for any vaginal or cervical erosions, areas of tenderness, or purulent or bloody discharge. A bimanual examination may show uterine or ovarian enlargement with the presence of tumors or cysts. The examiner should assess for signs and symptoms of androgen excess such as abnormal hair growth (hirsutism), voice changes, acne, frontal balding, central obesity and clitorimegaly. (See table 1 for the clinical presentation associated with PCOS).
Diagnosis

The diagnosis of PCOS is usually determined by the combination of clinical, ultrasonographic and biochemical criteria. Ultrasound criteria for polycystic ovaries include 10 or more cysts measuring 2-8 mm in diameter arranged peripherally around a dense core of stroma or scattered through an increased amount of stroma (Kyei-Mensah, Zaidi, & Campbell, 1996) (See figure 1). The use of ultrasound as a diagnostic criterion for PCOS is not universally accepted. Polson, Wadsworth, Adams, & Franks (1988) found that 20% of women who had polycystic ovaries had no other clinical features of PCOS, while 86% of women with irregular menses had polycystic ovaries. Either polycystic ovaries on ultrasonography, hirsutism, or hyperandrogenemia are needed to make the diagnosis of PCOS (Franks, 1998).

Treatment

The management of women with PCOS is usually symptomatic according to the presence of irregular menses, hirsutism, or infertility. Typically, women with irregular menses are treated with combined oral contraceptives, which help to increase the sex hormone binding globulin while decreasing androgen secretion. This results in decreased levels of circulating free testosterone. If the patient is obese, the pill may be unsuitable due to possible exacerbation of insulin resistance (Hopkinson et al., 1998).

Hirsutism is found in 70% of the patients with PCOS (MacKay, 1998). Normally, circulating testosterone is converted to dihydrotestosterone (DHT) in the skin which stimulates the hair follicle. Dihydrotestosterone levels are elevated in hirsutism. Hirsutism may be improved by hair removal or by the use of the antiandrogens. Hair removal techniques that can be recommended include shaving, depilatories, waxing,
electrolysis, and bleaching. Spironolactone or the combination of cyproterone acetate (available in Europe) and ethinyl estradiol work by binding DHT to its receptor at the hair follicle (Hopkinson et al., 1998; Franks, 1998). In using the antiandrogens, it takes three months for benefits to be seen, and excessive hair growth returns with cessation of therapy. Neither drug should be used if the patient is trying to become pregnant, and cyproterone acetate may exacerbate menses irregularity.

If a woman is having irregular menses but does not wish to become pregnant, medroxyprogesterone acetate can be given every day for the first ten days of each month (MacKay, 1998). This will prevent endometrial hyperplasia by causing regular shedding.

Infertility may be improved by clomiphene citrate, an antiestrogen, which helps in stimulating ovulation by enhancing the secretion of follicle stimulating hormone and therefore, inhibits the estrogen mediated negative feedback loop at the hypothalamus. Clomiphene may cause multiple births and, if used for more than six months, is associated with an increased risk of ovarian cancer (Hopkinson et al., 1998). The addition of dexamethasone 0.5 milligrams at bedtime may increase the likelihood of ovulation by suppressing the adrenocorticotrophic hormone (ACTH) and circulating adrenal androgens (MacKay, 1998).

For women who fail to ovulate on clomiphene, the use of gonadotropins may be considered. The combination of gonadotropins and human chorionic gonadotropin (hCG) results in a stimulation of ovarian follicular maturation. This results in an increased rate of ovulation and pregnancy rates of 50-70% within 6-12 months of therapy (Donesky & Adashi, 1996). Women with PCOS are more resistant to gonadotropin therapy than those who are hypo-estrogenic. Gonadotropin therapy includes increased
risk for medical complications including multiple births and ovarian hyperstimulation syndrome. It also is costly and requires close monitoring.

Nestler and Jakubowicz (1996) found that metformin decreased serum insulin concentrations, thereby decreasing free testosterone and ovarian cytochrome P450c17a activity in obese women with PCOS. It has also been found that by using metformin in obese women with infertility, the ovulatory response to clomiphene can be improved by decreasing insulin secretion (Nestler, Jakubowicz, Evans, & Pasquali, 1998).

For patients who fail the treatment of infertility with medication therapy, laparoscopic ovulation induction may be a possibility. This procedure works by destruction of ovarian stromal elements causing a fall in local and circulating androgens and estradiol levels. This affects the negative feedback mechanism by allowing a normalization of the LH/FSH ratio to occur and, therefore, causes follicular development to proceed to ovulation. The successfuleness of this procedure improves, if there are no other infertility factors other than the anovulation related to PCOS (Donesky & Adashi, 1996). Risk factors for this procedure include adhesion formation and ovarian atrophy.

Obesity is present in 50% of women with PCOS (Marantides, 1997). Weight reduction, through dietary modifications and exercise, is associated with an improvement in insulin resistance, ovulation, and regular menses (Hopkinson et al., 1998). Table 2 specifically addresses the history, physical, abnormal laboratory findings, and treatment plan of PCOS.

Differential Diagnosis

Anovulation in the reproductive years can be related to premature menopause, rapid weight loss, obesity, or excessive physical exercise. Anovulation can occur up to
six months after oral contraceptives are discontinued. Prior to an endocrine work-up, pregnancy should be ruled out. When amenorrhea has been present for six months or longer without a diagnosis, FSH, LH, prolactin, TSH, testosterone, and DHEAS levels should be evaluated (MacKay 1998). A 75-g oral glucose-tolerance test is also recommended due to the large number of patients with impaired glucose tolerance and NIDDM (Franks, 1995). The differential diagnosis should include diseases of the pituitary and adrenal glands such as hyperprolactinemia, acromegaly, and adrenal hyperplasia. Androgen secreting tumors of the ovary or adrenal gland should also be considered.

Adrenal hyperplasia can be identified by a DHEAS level > 700 ug/dL. An ovarian or adrenal neoplasm can be identified by a serum androstenedione level > 1000 ng/dL. A late-onset 21-hydroxylase deficiency can be identified with a baseline 17-hydroxyprogesterone level > 300 ng/dL or a stimulated level over 1000 ng/dL. Ovarian failure can be identified by an elevation of FSH and LH levels (Fitzgerald, 1998). Cushing’s syndrome and thyroid abnormalities should also be ruled out.

Sensitivity/Specificity

An elevated free testosterone level, defined by a free androgen index, is the most sensitive biochemical marker of PCOS. An elevated LH level is now a less favored diagnostic test (Hopkinson et al., 1998). Adams, Polson, & Franks (1986) found that 87% of women with oligomenorrhea and 26% of women with amenorrhea had polycystic ovaries. They stated that ovarian appearance correlated with menstrual history and that ultrasonography can be used as a reference test against which to evaluate other diagnostic criteria such as an elevated LH or testosterone level.
Adams, Polson, & Franks (1986), found that 90% of 173 patients with ultrasound evidence of polycystic ovaries had at least one other endocrine abnormality suggestive of PCOS confirming the specificity of ultrasound. The diagnostic accuracy of polycystic ovaries was improved to 95% when transvaginal rather than transabdominal ultrasound was used (Kyei-Mensah, Zaidi, & Campbell, 1996).

Cost Effectiveness

Patients should fast prior to drawing an insulin level, although this is not a necessary test in the diagnosis of PCOS. The patient does not need to be fasting for any labwork. A pelvic ultrasound requires the patient to drink 32 ounces of water prior to the test. The cost of a pelvic ultrasound ranges from $160.00 to $189.00. (See table 3 for estimations of price ranges of laboratory tests.)

Patient Teaching/Preparation

Obesity is associated with worsening of symptoms in PCOS and, therefore, weight loss should be strongly recommended in obese patients. Weight loss can be difficult, so the patient should be advised to exercise regularly and to eat a diet high in fiber and low in refined carbohydrates to help improve the hyperinsulinemic state (Conway, 1996).

Holte (1996) reported a study in which 13 obese, severely insulin-resistant women with PCOS underwent a low calorie weight-reduction program and lost an average of 25 pounds. The weight loss resulted in a loss of truncal-abdominal fat, improved insulin sensitivity, and decreased free fatty acid and testosterone levels. A decrease in body fat will also help to restore ovulation by decreasing the conversion of androgens to estrone (MacKay, 1998). Women with PCOS have an increased risk for ovarian cancer which
may be related to the increased levels of LH (Schildkraut, Schwingl, Bastos, Evanoff, & Hughes, 1996).

Ehrmann, et al. (1999) found that of 122 women with PCOS ≥ 2 years postmenarche, 35% had impaired glucose tolerance and 10% had NIDDM. Furthermore, the chances of converting from IGT to NIDDM were increased 5-to 10-fold in PCOS. The issue of glucose intolerance was further complicated by upper-body obesity commonly found in those with PCOS, which is known to increase the risk of NIDDM. PCOS patients with hyperandrogenemia and hyperinsulinemia also have an increased risk for hyperlipidemia and cardiovascular disease, which includes hypertension, coronary artery disease and atherosclerosis (Guzick et al., 1995). Risk factors for cardiovascular disease include central obesity, glucose intolerance, increased triglycerides, and low levels of HDL, which are all found in women with PCOS.

For women with hirsutism, it should be recommended that they first try hair removal modalities, rather than medications. If medications are used, warn patients that it may take up to six months for improvements to occur and that excessive hair growth will return when the medications are discontinued.

Women trying to conceive with clomiphene citrate should be advised that 70-80% of women have improved ovulatory cycles, but only 50% will conceive (Donesky & Adashi, 1996). Women should also be informed that multiple births are a side effect of clomiphene citrate therapy.

Summary

Polycystic ovary syndrome is a complex endocrine disorder of hypothalamic-pituitary dysfunction that presents with anovulation, hirsutism, and infertility. Women
with PCOS have increased risk for developing NIDDM, dyslipidemia, and premature cardiovascular disease. Because of its vague presentation and potential for numerous complications, PCOS should be evaluated carefully. Unfortunately, there is no cure for PCOS and the treatment has numerous limitations. Weight loss in an obese patient may greatly improve the patient’s response to treatment and should be encouraged.
References


Table 1.

**Clinical Presentation of PCOS**

- **Hyperandrogenism Signs and Symptoms**
  - Hirsutism
  - Acne
  - Male-pattern alopecia
  - Central obesity
  - Voice changes
  - Clitorimegaly

- **Anovulation Signs and Symptoms**
  - Amenorrhea or Oligomenorrhea
  - Dysfunctional bleeding
  - Infertility
Table 2.

**Algorithm/Pathway of Polycystic Ovary Syndrome**

<table>
<thead>
<tr>
<th>H &amp; P (positive findings include):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hirsutism</td>
</tr>
<tr>
<td>• Acne</td>
</tr>
<tr>
<td>• Male Pattern Alopecia</td>
</tr>
<tr>
<td>• Amenorrhea or Oligomenorrhea</td>
</tr>
<tr>
<td>• Infertility</td>
</tr>
<tr>
<td>• Central Obesity</td>
</tr>
<tr>
<td>• Ovarian enlargement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal Laboratory/Diagnostic Tests (any or all may be found):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elevated Free Testosterone Level</td>
</tr>
<tr>
<td>• Elevated LH:FSH Ratio</td>
</tr>
<tr>
<td>• Hyperinsulinemia</td>
</tr>
<tr>
<td>• On ultrasound, normal sized or enlarged ovaries with or without the classical &quot;necklace&quot; arrangement of follicles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment (should be symptomatic):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom:</td>
</tr>
<tr>
<td>• Irregular Menses: Oral contraceptives</td>
</tr>
<tr>
<td>• Hirsutism: Antiandrogen or manual hair removal</td>
</tr>
<tr>
<td>• Infertility: Clomiphene citrate, Gonadotropin or Laparoscopic ovulation induction</td>
</tr>
<tr>
<td>• Obesity: Dietary modifications; Exercise</td>
</tr>
</tbody>
</table>
Table 3.

**Laboratory test price ranges**

Laboratory test ranges based on prices from the University of Washington and Pathology Associates Medical Laboratories, Spokane, Washington.

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>$21.60-$58.80</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>$61.65-$76.75</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>$61.55-$128.90</td>
</tr>
<tr>
<td>LH</td>
<td>$31.00-$50.95</td>
</tr>
<tr>
<td>FSH</td>
<td>$31.00-$50.95</td>
</tr>
<tr>
<td>Prolactin</td>
<td>$41.80-$51.20</td>
</tr>
<tr>
<td>Free T4</td>
<td>$37.30-$42.15</td>
</tr>
<tr>
<td>TSH</td>
<td>$25.70-$43.95</td>
</tr>
<tr>
<td>DHEAS</td>
<td>$52.65-$115.00</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone</td>
<td>$27.00-$104.95</td>
</tr>
</tbody>
</table>
The criteria for a diagnosis of polycystic ovaries based on ultrasonographic data include bilateral ovarian enlargement (>9 cm in maximal diameter), 10 or more follicles 2 to 8 mm in diameter per ovary, and increased density and area of stroma.