

Upcoming Events

- A reproductive psychologist will be joining our staff in the spring.
- New satellite office in Leesburg, Florida.
- Reproductive Health Fair for patients October 2002.

Classes and Workshops are available throughout the year. Call the Reproductive Health Institute to get a list of programs.

Mental Health Counseling is available for coping strategies and stress reduction. Call the Reproductive Health Institute for more information.

Reproductive Health Institute
Part of Arnold Palmer Hospital
for Children & Women
22 Underwood Street
Orlando, Florida 32806
407 649-6995 or 800 411-8504

Visit us at
www.arnoldpalmerhospital.org/fertility
or e-mail us at rhi@orhs.org.

Polycystic Ovarian Syndrome and Insulin Resistance

Introduction

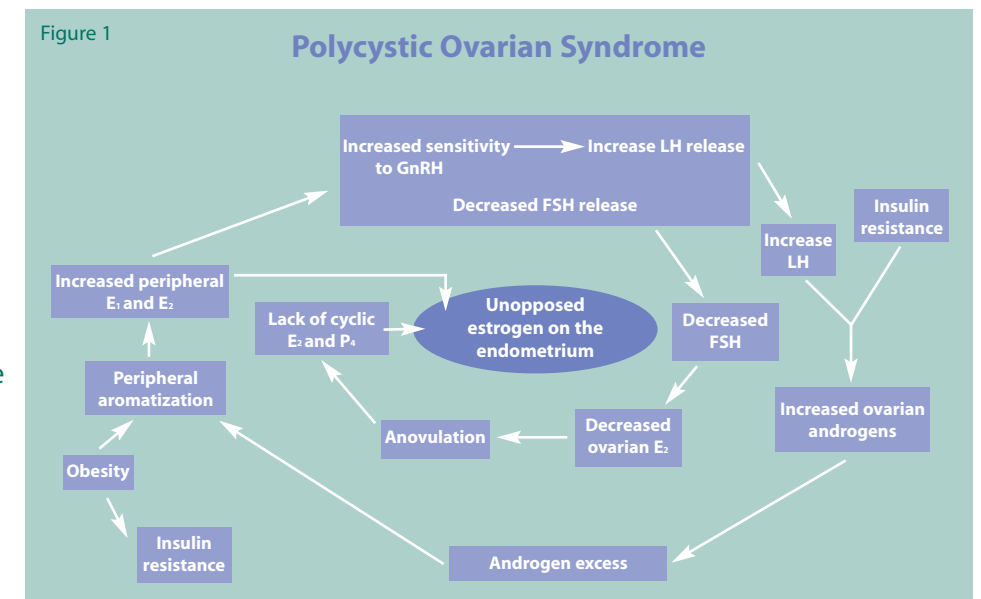
Polycystic Ovarian Syndrome (PCOS) is the most common endocrine abnormality in reproductive-aged women affecting approximately 5-10% of this population (NEJM 1995;333:853). The classic triad of this syndrome consists of chronic anovulation, hirsutism and obesity. PCOS was first discovered by Stein and Leventhal (Am J Obstet Gynecol 1935;29:181) and its management has confused clinicians ever since. The exciting news recently involves understanding the contribution of insulin resistance to the etiology and treatment of PCOS. This newsletter will review the endocrinopathy and medical consequences of PCOS as well as examine the current understanding of insulin resistance and the use of insulin sensitizing agents.

with an increase in LH secretion resulting in increased ovarian androgen production by the ovarian thecal cells. The ovarian "androgen excess" has several effects: a) inhibiting follicle development and estradiol production; b) stimulating excess terminal hair production (hirsutism) and c) increasing peripheral conversion of estradiol to estrone. Consequently, FSH production is inhibited thereby further preventing follicle development and ovulation. Additionally, estrone proliferates the endometrium unopposed and increases the risk of endometrial hyperplasia and possibly cancer. To summarize, PCOS is perpetuated by tonic

Mission and Goals

The Reproductive Health Institute provides state-of-the-art services for the treatment of reproductive hormonal disorders and infertility with advanced reproductive technologies.

Our mission is to provide comprehensive reproductive healthcare for the people in our community through consultation, diagnosis, education and treatment in a compassionate environment.



Continued, inside

elevations of LH resulting in hyperandrogenemia and chronic anovulation.

Diagnostic Criteria

PCOS can be diagnosed clinically in women who present with oligomenorrhea (menstrual intervals >35 days), hyperandrogenism and obesity (after ruling out other endocrine disorders). However, most women with PCOS do not exhibit all of these features and there is a considerable controversy about the definition and required criteria for the diagnosis. The results of a consensus conference of the National Institute of Health on PCOS in April 1990 are shown in Table 1. Thus, the minimal criteria include chronic anovulation and hyperandrogenism, and the diagnosis does not require pelvic ultrasound to evaluate morphology for PCOS “appearing” ovaries.

Clinical Presentation and Medical Consequences

Infertility

Approximately 40% of female infertility factors result from ovulation dysfunction. Women with PCOS may experience a wide range of ovulation dysfunction, from oligo-ovulation to anovulation. Other factors appear to be involved, as PCOS women may have a lower rate of conception in response to ovulation inducing agents (clomiphene citrate, gonadotropins) in comparison to women with

Major	Minor
<ul style="list-style-type: none"> • Ovulatory dysfunction • Clinical evidence of hyperandrogenism and/or hyperandrogenemia • Exclusion of related disorders 	<ul style="list-style-type: none"> • Insulin Resistance • Pubertal onset of hirsutism & obesity • LH/FSH > 2 • PCOS “appearing” • Hyperandrogenic oligo-ovulation

Dunaif (ed) Polycystic Ovary Syndrome Boston: Blackwell 1992:377

hypothalamic amenorrhea. Many studies have also described the almost two fold increased miscarriage rate in PCOS (which may be due to elevated CH).

Abnormal Uterine Bleeding and Endometrial Hyperplasia

Due to chronic anovulation, women with PCOS usually have irregular menses. These women are exposed to continuous unopposed estrogen stimulation of the endometrium. They are deficient in progesterone secretion, which is needed for endometrial differentiation and withdrawal bleeding. Thus, they are at risk for dysfunctional uterine bleeding, endometrial hyperplasia and possibly carcinoma.

Hyperandrogenism

The clinical features of androgen excess in women with PCOS include hirsutism, acne, male pattern balding (alopecia), and rarely, signs of virilization including deepening of the voice, increased muscle mass, and clitoromegaly. Hirsutism occurs in approximately 70 - 80% of PCOS patients (Endocrinol & Metab Clinics, 1999;28:398) and is defined as the conversion of vellus (soft, unpigmented) to terminal (thick,

pigmented) in a male pattern distribution along sex dependent regions, e.g., upper lip, peri-areola, and lower abdomen. There is substantial ethnic variability: up to 33% of non-Scandinavian and non-Asian women have some evidence of hirsutism (Obstet Gynecol Surv, 1999;54:405); Asian women may have significant hyperandrogenism without impressive skin manifestations. Virilization is rare and women who present with rapidly progressive masculinizing signs should be evaluated for androgen tumors of the adrenal gland or ovary.

Obesity

Obesity is a common, but not necessary, finding in at least 50 to 65% of women with PCOS. Patients usually have central (android) body fat distribution. Android obesity, which is characterized by increased waist-to-hip ratio (>0.80), is correlated with increased plasma testosterone, decreased sex-hormone-binding globulin (SHBG), hyperinsulinemia, impaired glucose tolerance, and dyslipidemias (Obstet Gynecol Surv 1999;54:406, PCOS; Cambridge, MA: Blackwell Scientific, 1992 pp 359-374).

Insulin Resistance and Diabetes

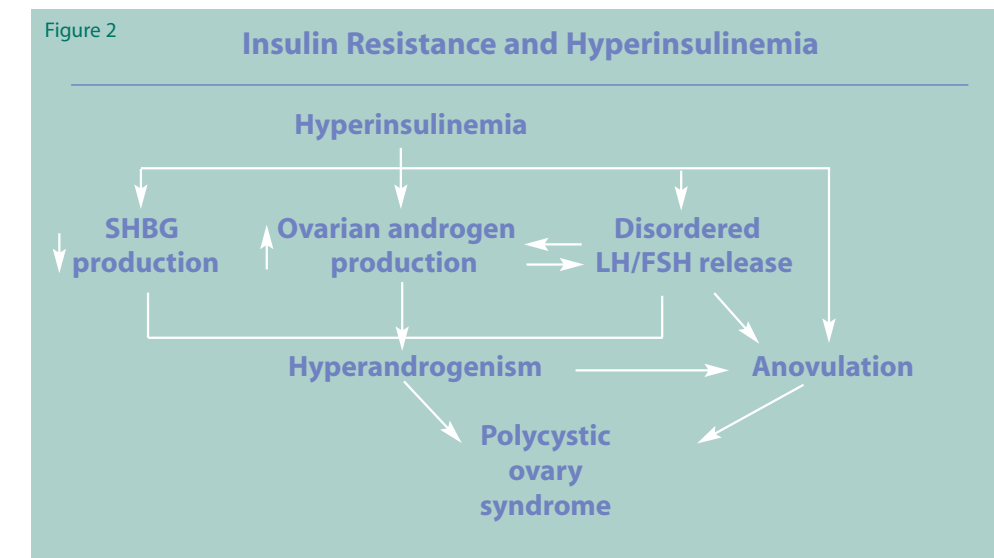
Many women with PCOS exhibit insulin resistance and hyperinsulinemia (Figure 2). Although it is more commonly associated with obesity, it is also found in normal-weight women with PCOS (*J. Clin Endocrinol & Metab* 1996;81 pp. 2854-2964). Because of insulin resistance, women with PCOS are at increased risk for impaired glucose tolerance and diabetes mellitus. A recent study found up to 40% of obese, reproductive-age women with PCOS had impaired glucose tolerance and that 7.5% had diabetes mellitus. In addition, 15% of normal-weight women with PCOS had impaired glucose tolerance and 1.5% had diabetes, a rate almost three times that of the general population. The pathogenesis of insulin resistance remains unclear. It has been reported that insulin resistance may be related to decreased insulin receptor autophosphorylation in about 50% of women with PCOS (*Endocrinol & Metab Clin*; 28(2), 6/99 p. 350). If untreated, insulin resistance leads to diabetes in approximately one-third of patients.

Evaluation

Polycystic ovary syndrome is primarily a clinical diagnosis, and laboratory findings should only be used to support the clinical testing and rule out other serious disorders.

Evaluation should include measurement of thyroid-stimulating hormone (TSH), prolactin, and in some cases, morning 17alpha hydroxyprogesterone to rule out late-onset adrenal hyperplasia. Patients, regardless of age, with long standing unopposed estrogen stimulation should undergo an endometrial biopsy due to the risk of hyperplasia.

Insulin resistance can be evaluated by measuring fasting plasma insulin levels or fasting morning plasma glucose-to-



insulin ratio (<4.5 is highly sensitive and specific for insulin resistance) (*J. Clin Endocrinol Metab* 1998; 83 pp. 2694-2698), as well as fasting glucose level or 2-hour glucose tolerance test (GTT) (Table 2). (Endocrinology and Metabolism clinics of North America, June 1999, 397-407).

The diagnosis of PCOS does not require the presence of polycystic ovaries on ultrasound since approximately 20% of fertile women may have polycystic appearing ovaries (Lancet, 1988; 1, pp. 870-872).

Management

Lifestyle Changes

Weight reduction, diet and exercise are recommended for all women with PCOS.

Weight loss typically results in increased insulin sensitivity, reduced hyperandrogenism, fewer lipid abnormalities and better cardiovascular health. Some studies have also shown a 5-10% loss in body weight may result in a return of ovulatory cycles and a higher spontaneous pregnancy rate. (J. Clin Endocrinology & Metabolism 1999; Vol 84, 1470).

Pharmacologic Treatment

Pregnancy Not Desired:

Monthly *progestin* therapy can be used to prevent abnormal endometrial proliferation by inducing withdrawal bleeding. Another option for these women is to use low dose *oral contraceptive pills* (OCP) to regulate the menstrual cycle and provide contraception. The estrogen component of OCPs increases levels of SHBG to lower free testosterone and improve hirsutism and acne whereas the progestin component prevents endometrial hyperplasia.

Pregnancy Desired:

Antiandrogens may be combined with oral contraceptive pills for the treatment of hirsutism and acne. The most commonly used agent is

spironolactone because of its safety and low cost. Several months of treatment may be needed before an improvement in hirsutism is seen. *Clomiphene citrate* is the first line of therapy. The dose of clomiphene can be increased, until ovulation occurs,

	Impaired Glucose Tolerance	
75gm 2hr glucose tolerance test	fasting 2 hour	110-126* 140-200
Fasting glucose to insulin ratio	<4.5	
Fasting insulin level	> 20	

*1997, ADA; 1998, WHO

up to 150 mg/day and then maintained for four to six cycles. Approximately 80% of women with PCOS ovulate in response to clomiphene, but only about 50% of them become pregnant (Fertility and Sterility 1984; 42:499).

Current *insulin sensitizing agents* include *metformin* and *thiazolidenediones*. *Metformin (Glucofage)* works by activating glucose transporters which allow passage of glucose into hepatic and muscle cells thereby decreasing peripheral insulin resistance. *Metformin* does not stimulate insulin release and, when given alone, does not cause hypoglycemia (American Society for Reproductive Medicine, a practice committee report, April 2000). In a randomized trial, obese women with PCOS were given 500 mg of metformin three times daily for 35 days or placebo. Thirty-four percent of the women in the metformin group ovulated spontaneously during treatment with metformin alone, as compared with only 4% in the placebo group.

The subjects who remained anovulatory after 35 days, continued into the second phase of the trial, in which clomiphene was added to both groups. Ninety percent of women who received combined metformin and clomiphene ovulated compared to only 8% in the group given placebo and clomiphene. (NEJM, 6/25/98, pp.1876-1880). Currently, it is recommended to discontinue Metformin when pregnancy occurs.

Prior to initiating metformin, the patient should be screened for medical problems. Contraindications of therapy are listed in Table 3. Side effects of metformin are most commonly gastrointestinal including nausea, vomiting, diarrhea and abdominal bloating. Reducing the dosage from one to two weeks may improve symptoms. Some patients ultimately may not tolerate this medication.

Table 3 Use of Metformin

Contraindications

- Kidney disease (Cr>1.3)
- Liver disease
- Cardio-respiratory disease
- Severe infection
- Alcohol abuse
- History of lactic acidosis
- IV Contrast dye use
- Cimetidine therapy

Surgical Options

In patients requiring ovulation induction and who are resistant to clomiphene citrate, ovarian surgery has been an effective therapy. Laparotomy with bilateral ovarian wedge resection has been replaced by the more modern laparoscopy with bilateral ovarian diathermy. By "drilling" holes in the ovarian stroma utilizing electrocautery or laser, surgery has allowed for an approximate 84% ovulation induction rate and 56% pregnancy rate (Fertil Steril 1995;63:439-463). The maintenance of ovulation has been demonstrated for up to 20 years in the majority of patients (Fertil Steril 1998;69:697-701).

The *Thiazolidenediones* are under active investigation for treatment of PCOS. They act by binding to peroxisome proliferation activator receptor gamma, which decreases peripheral insulin resistance. The available drugs in this class include *rosiglitazone (Avandia)* and *pioglitazone (Actos)*. *Troglitazone (Rezulin)* was removed from the market due to several reports of hepatic failure. *Thiazolidenediones* are not recommended in women desiring pregnancy due to concerns of teratogenicity.

Summary

PCOS is a chronic condition that can be successfully managed with close surveillance (Table 4). Approaches are directed at preventing potential long-term consequences of chronic anovulation (abnormal uterine bleeding and endometrial hyperplasia), the metabolic abnormalities associated with the syndrome (insulin resistance and diabetes), *treating* infertility, as well as improving the external manifestations of hyperandrogenism (hirsutism and acne).

Table 4 Goals of Therapy in PCOS

<p>Improve reproductive function</p> <ul style="list-style-type: none"> Decrease risk for endometrial cancer 	<p>Promote weight loss</p> <p>Reduce risks of insulin resistance</p> <ul style="list-style-type: none"> Glucose intolerance Dyslipidemia Hypertension Atherogenesis
<p>Reduce serum androgens</p>	