

# THE CENTER FOR REPRODUCTION & WOMEN'S HEALTH CARE

*Robert B. McWilliams, MD*

## **POLYCYSTIC OVARIAN SYNDROME and its association with FERTILITY**

Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorders of women of reproductive age. Affecting approximately 6-10% of all premenopausal women and approximately 70-90% of women with irregular menstrual cycles, the classic symptoms of this disorder consist of irregular periods, infertility, and excessive body and facial hair. As a consequence of the overproduction of androgens (male hormones) by the ovaries, additional symptoms of acne, obesity, and male-pattern hair loss are seen together with symptoms of anovulation like heavy menstrual flow and erratic, unpredictable onset of menses. Some patients may demonstrate very mild or no symptoms of this disorder, complaining only of irregular cycles. Other patients may demonstrate all of the classic symptoms mentioned above.

The name, polycystic ovarian syndrome is derived from the morphologic (appearance) alterations that occur in the ovary. Failure to ovulate (to rupture and release ovulatory eggs) on a monthly basis yields ovaries that are literally, "covered with ovarian cysts." This failure to ovulate healthy eggs results in infertility and a higher rate of miscarriage after a positive pregnancy test.

Despite our understanding of this most intriguing endocrine disorder of women, scientists have been searching for an association among the many facets of PCOS. Unfortunately, the pathophysiology of the various disorders remains unknown. In the past, it was common for a woman with infertility to have this diagnosis made during an infertility evaluation. Today, if the consequences of this disorder are left unattended, these patients, infertile or not, will develop severe clinical problems.

A reduction in a woman's life expectancy occurs with no treatment of this disorder as a consequence of cardiovascular disease and diabetes mellitus. Recent research has found growing concern that this syndrome is also associated with hyperinsulinemia (excess production of insulin by the pancreas), insulin resistance, dyslipidemia (abnormality of metabolism of fats), and hypertension. Risks of developing type 2 diabetes (noninsulin-dependent) and possibly, premature cardiovascular disease is higher in these patients with insulin resistance. Other consequences of anovulation include carcinoma of the endometrium and possibly carcinoma of the breast. These facts have lead to a new attitude towards this common female problem highlighting its legitimate place in today's "modern preventive health care of women."

Insulin resistance, characterized by a decrease in the ability of insulin to stimulate glucose uptake to muscle and fat cells, as well as to inhibit glucose production by the liver is a common feature of women with PCOS. **Up to 60% of women with PCOS** demonstrate some degree of impaired glucose tolerance as a result of insulin resistance. A sign of severe insulin resistance exists known as acanthosis nigricans, a condition in which dark velvety patches appear on the skin. These areas are usually seen around the back part of the neck ("ring around the collar") and in other areas of the body where the skin folds on itself forming creases. It appears likely that an inherent, probably genetically determined ovarian defect is present in women with PCOS, which makes the ovary

susceptible to insulin stimulation of androgen (male-like hormone) production. The insulin resistance and hyperinsulinemia are primary events in PCOS that somehow lead to hyperandrogenism and the subsequent reproductive endocrine abnormalities.

It goes without saying that the clinician must recognize the clinical impact of PCOS and undertake therapeutic management of all anovulatory patients to avoid these unwanted consequences. Use of birth control pills, insulin sensitizing drugs, changes in life style patterns, gonadotropin releasing hormone agonists, advanced diagnostic techniques and assisted reproductive technologies are currently increasing our understanding of this disorder. Our hope is to initiate preventative measures early in young women's lives (teenage years) that yield increased longevity with healthier and more reproductive outcomes.

Diagnosis of PCOS usually follows a high sense of suspicion in women with irregular cycles who demonstrate mild forms of hyperandrogenism and are having difficulty getting pregnant. To confirm the diagnosis, blood testing of "the brain to ovary and ovary to brain signals" are assessed on cycle days 3, 4 or 5. Measurement of FSH (follicle stimulating hormone), LH (luteinizing hormone), and testosterone give a characteristic pattern for the diagnosis of PCOS on most occasions. The level of LH is normally equal to FSH in women without PCOS. With this disorder, LH is often higher than FSH, up to 2-3 times, as well as high testosterone levels ( $> 50$  ng/dl) revealing high ovarian production. Checking serum progesterone levels on cycle days 21-23 to confirm ovulatory function is unusually low ( $< 4$  ng/dl), indicating ovulatory problems. Your clinician might also recommend an ultrasound evaluation of the ovaries.

Insulin resistance can be determined by obtaining a blood sample after a 12 hour fast for insulin and glucose. A glucose/insulin ratio of  $< 7.0$  will be used to define insulin resistance. Other tests that might be used to help establish the diagnosis include a C-peptide and a glycosolated hemoglobin (HbA1C).

All right, now that I have your attention, how does PCOS affect a woman's fertility? By affecting ovulation! These women do produce estrogen from the ovaries in addition to testosterone, but the levels of estrogen are lower than expected at the time of ovulation. Because of the high level of LH and testosterone, follicular suppression is caused within the ovary yielding poor or no ovulation with subsequent loss of progesterone. Without a properly developed, healthy, fertilizable egg and without estrogen and progesterone to secure a well-developed endometrial bed for the ensuing pregnancy, infertility results. In some women, an attempt to ovulate a poorly developed egg late in the cycle yields a miscarriage from "a blighted ovum."

And how does insulin resistance play a role in infertility? Again, by affecting ovulation. Researchers now have found that high levels of insulin can stimulate the activity of enzymes that are pivotal to the manufacture of androgens in the ovary. They have also discovered alterations or defects of these same enzymes that make them susceptible to overstimulation by insulin. Consequently, high levels of insulin or overstimulation of androgen receptors by insulin leads to follicular atresia (suppression) of early developing eggs long before ovulation.

Therapeutic options of PCOS depend on the severity of symptoms and the woman's goal. Does the patient desire elimination of excess hair and/or acne? Does she desire regular periods with normal bleeding? Does she desire pregnancy? Is she at high risk of the metabolic abnormalities associated with this disorder?

Many treatment plans exist for PCOS. Among the most common are 1) weight loss, 2) hormonal manipulations, 3) surgical treatments, 4) steroid supplementation, 5)

spironolactone, and more recently, 6) insulin sensitizing medications. Your particular treatment plan will depend on your goals.

Today, we are truly entering a new era in our understanding and management of women with polycystic ovaries and hyperandrogenism. We now have a real opportunity “to make a difference in others lives” by affecting the quality and quantity of life to be experienced by these patients. Let us not only correct specific clinical consequences of anovulation but, let us also reduce major adverse effects on overall health.

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**Use of Rosiglitazone maleate (Avandia)  
in the Treatment of  
Polycystic Ovarian Syndrome (PCOS) with Insulin Resistance**

**1. PCOS and Insulin Resistance**

Polycystic Ovarian Syndrome one of the most common endocrine disorders of women of reproductive age. Classic symptoms consist of hyperandrogenism (hirsutism, acne) together with symptoms of anovulation (infertility and oligomenorrhea). Recent research has found growing concern that this syndrome is also associated with hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension. Risks of developing type 2 diabetes (noninsulin-dependent) and possibly premature cardiovascular disease is higher in these patients with insulin resistance.

Insulin resistance, characterized by a decrease in the ability of insulin to stimulate glucose uptake to muscle and fat cells, as well as to inhibit glucose production by the liver is a common feature of women with PCOS. Up to 60% of women with PCOS demonstrate some degree of impaired glucose tolerance as a result of insulin resistance. It appears likely that an inherent, probably genetically determined ovarian defect is present in women with PCOS which makes the ovary susceptible to insulin stimulation of androgen (male-like hormone) production. The insulin resistance and hyperinsulinemia are primary events in PCOS that somehow lead to hyperandrogenism and the subsequent reproductive endocrine abnormalities.

**2. Nature of the Drug**

Avandia (rosiglitazone maleate), an oral hyperglycemic (elevated blood sugar) agent which acts primarily by improving the cells response to insulin, is manufactured by GlaxoSmithKline Pharmaceuticals. Rosiglitazone maleate is one of a unique class of drugs that exerts direct effects on insulin resistance. It appears to enhance insulin action without directly stimulating insulin secretion or affecting glucose levels. Its effects help lower the elevated insulin levels in the blood stream of patients with insulin resistance. Avandia has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because of its insulin-dependent mechanism of action, Avandia is approved by the FDA for the management of type II diabetes (non insulin dependent diabetes mellitus (NIDDM)) also known as adult onset diabetes. It is important to understand that only a few small studies concerning the use of Avandia in PCOS have been published or presented, and conclusive data regarding outcome, patient risks and complications, while currently being collected, is not yet available. For this reason, this information is intended to help inform you about this medication.

**3. Potential Benefits**

Clinical studies demonstrate that Avandia improves insulin-sensitivity in insulin-resistant patients. The effects occur without weight loss. Treatment of PCOS patients with rosiglitazone maleate led to improvement of insulin resistance and hyperinsulinemia, with the concomitant reduction of elevated testosterone and LH levels toward the normal range. In some of these women, ovulation also occurred during the period of drug therapy. The advantage of Avandia over traditional therapies for the treatment of PCOS is two-fold; 1) it corrects both metabolic and endocrinologic aberrations; and 2) it permits resumption of normal endogenous ovulatory function, with little or no risk of ovarian hyperstimulation or multiple gestation.

#### **4. Method of Administration**

Avandia is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. It is absorbed rapidly after oral administration, the time for maximum plasma concentration occurs within 2 to 3 hours. Food increases the extent of absorption by 30 % to 85%; thus Avandia should be taken with a meal to enhance systemic drug availability.

Avandia has other unique advantages, including once-a-day administration, a low incidence of minor side effects, no known drug interactions, hepatic metabolism and secretion, and potent antioxidant properties

#### **5. Risks and/or Side Effects**

Avandia is contraindicated in women with certain underlying medical disorders. Avandia has been associated with elevated liver function tests, and in extremely rare cases, hepatic necrosis. Rare cases of hepatic injury have been reported. Therefore, serum liver function tests are to be followed monthly for the first eight months of therapy, every 2 months for the remainder of the first year of Rezulin treatment, and periodically thereafter. Rezulin will not be initiated if there is any evidence of liver disease.

In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. The use of Rezulin can cause resumption of ovulation in women taking oral contraceptives (OC). Therefore, a higher dose of OC or an alternative method of contraception should be considered. These patients may be at risk for pregnancy.

Another concern with this drug is possible teratogenic effects. Although this medication has no known human teratogenic effects, this reflects the lack of substantial experience in reproductive-aged women with Avandia. A prospective registry is now in place to monitor birth outcomes following Avandia exposure.

#### **6. Pre-treatment Testing**

At the initial screening, hyperinsulinemic insulin resistance will be determined by obtaining a blood sample after a 12 hour fast for insulin, glucose and C-peptide levels. A glycosolated hemoglobin (HbA1C) will also be determined. A glucose/insulin ratio of < 7.0 will be used to define insulin resistance. A hepatic profile will be monitored at monthly intervals to follow liver function.

#### **7. Alternative Therapy**

The correction of hyperandrogenism in women with PCOS may be achieved by interventions which improve insulin sensitivity and reduce circulating insulin. Such measures include, but are not limited to weight loss, dietary modifications and insulin-sensitizing medications.

The use of anti-diabetic drugs in PCOS represents a novel use of these agents. The management of PCOS should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the insulin resistant patient with PCOS. This is not only important in the primary treatment of PCOS but in maintaining efficacy of drug therapy.

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## **Use of Metformin Therapy in the Treatment of Polycystic Ovarian Syndrome with Insulin Resistance**

### **1. PCOS and Insulin Resistance**

Polycystic Ovarian Syndrome one of the most common endocrine disorders of women of reproductive age. Classic symptoms consist of hyperandrogenism (hirsutism, acne) together with symptoms of anovulation (infertility and oligomenorrhea). Recent research has found growing concern that this syndrome is also associated with hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension. Risks of developing type 2 diabetes (noninsulin-dependent) and possibly premature cardiovascular disease is higher in these patients with insulin resistance.

Insulin resistance, characterized by a decrease in the ability of insulin to stimulate glucose uptake to muscle and fat cells, as well as to inhibit glucose production by the liver is a common feature of women with PCOS. Up to 60% of women with PCOS demonstrate some degree of impaired glucose tolerance as a result of insulin resistance. It appears likely that an inherent, probably genetically determined ovarian defect is present in women with PCOS which makes the ovary susceptible to insulin stimulation of androgen (male-like hormone) production. The insulin resistance and hyperinsulinemia are primary events in PCOS that somehow lead to hyperandrogenism and the subsequent reproductive endocrine abnormalities.

### **2. Nature of the Drug**

Metformin (Glucophage), an oral hyperglycemic (elevated blood sugar) agent which acts primarily by improving the cells response to insulin, is manufactured by Bristol-Myers Squibb Pharmaceuticals. Metformin is one of a unique class of drugs that exerts direct effects on insulin resistance without affecting insulin secretion. Metformin is known to increase peripheral glucose uptake with some reduction in basal hepatic glucose production. Its effects help lower the elevated insulin levels in the blood stream of patients with insulin resistance. Metformin has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because of its insulin-dependent mechanism of action, Metformin is approved by the FDA for the management of type II diabetes (non insulin dependent diabetes mellitus (NIDDM)) also known as adult onset diabetes. **It is important to understand that only a few small studies concerning the use of Metformin in PCOS have been published or presented, and conclusive data regarding outcome, patient risks and complications, while currently being collected, is not yet available. For this reason, this information is intended to help inform you about this medication.**

### **3. Potential Benefits**

Metformin treatment has been reported to decrease fasting insulin levels in nondiabetic obese women. Clinical studies have specifically examined changes in ovulatory function in women with PCOS on Metformin (Glucophage 500 mg three times per day with meals) and confirmed increased frequency of spontaneous ovulation, resumption of menstrual cyclicality, and an improved ovulatory response to clomiphene. Several previously infertile women with PCOS who were treated with Metformin for six months conceived and delivered healthy infants. The advantage of Metformin over traditional therapies for the treatment of PCOS is two-fold; 1) it corrects both metabolic and endocrinologic aberrations; and 2) it permits resumption of normal endogenous ovulatory function, with little or no risk of ovarian hyperstimulation or multiple gestation.

#### **4. Method of Administration**

Metformin (Glucophage) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. It is absorbed rapidly after oral administration with steady state plasma concentrations reached within 24-48 hours. Food slightly delays drug absorption thus Metformin should be taken with a meal to reduce adverse drug side effects.

#### **5. Risks and/or Side Effects**

Metformin, which has been in clinical use in the United States since 1995, can produce gastrointestinal symptoms which are dose-related and tend to resolve after several weeks. In the first few weeks of taking the medication, many people will often experience anorexia (loss of appetite), nausea, diarrhea or abdominal discomfort which usually resolves during continued treatment. Because gastrointestinal symptoms during therapy appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take Metformin with meals. Side effects can be minimized by starting with one pill (500 mg) daily for the first week with dosage increases made in increments of one tablet every week up to 3 pills (1500 mg) per day.

Metformin is contraindicated in women with certain underlying medical disorders. Rare and more serious adverse effects of Metformin therapy include lactic acidosis and pernicious anemia. Metformin should not be prescribed to patients with renal, hepatic, or major cardiovascular disease. Its use is contraindicated in renal impairment (creatinine greater than 1.4 or creatinine clearance less than 60%) or liver dysfunction. The risk of developing lactic acidosis is very low but some factors can increase your risk because they can affect kidney and liver function. If patients have an illness that results in severe vomiting, diarrhea, and/or fever, or if intake of fluids is severely reduced, they need to call their physician. Alcohol is known to potentiate the effect of Metformin and patients should be warned against excessive (all the time or "short-term binge") alcohol intake while taking Metformin. Furthermore, radiographic contrast studies with iodinated materials (e.g. hysterosalpingogram [HSG]) can lead to acute alteration of renal function so that patients in whom such a study is planned Metformin should be discontinued prior to the procedure and withheld for 48 hours. Treatment is reinstated only after renal function has been re-evaluated and found to be normal. Similarly, Metformin therapy should be temporarily suspended for any surgical procedure and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

In premenopausal anovulatory patients with insulin resistance, Metformin treatment may result in resumption of ovulation. Since these patients may be at risk for pregnancy, another concern with this drug is possible teratogenic effects. Although this medication has no known human teratogenic effects, this reflects the lack of substantial experience in reproductive-aged women with Metformin. While there are no well-controlled studies of safety during pregnancy, Metformin has been administered to a small number of women with diabetes throughout their pregnancies and no fetal abnormalities have been described. Metformin is a category B drug which means there is insufficient available human data but no teratogenic effects have been demonstrated in controlled animal studies. Until more data are available, administration of Metformin during pregnancy is not recommended.

#### **6. Pre-treatment Testing**

At the initial screening, hyperinsulinemic insulin resistance will be determined by obtaining a blood sample after a 12 hour fast for insulin, glucose and C-peptide levels. A glycosolated hemoglobin (HbA1C), CBC with differential and platelets, and urinalysis will also be evaluated. A glucose/insulin ratio of < 7.0 will be used to define insulin resistance. A comprehensive metabolic panel profile will be monitored at monthly intervals to follow renal and liver function.

## **7. Alternative Therapy**

The correction of hyperandrogenism in women with PCOS may be achieved by interventions which improve insulin sensitivity and reduce circulating insulin. Such measures include, but are not limited to weight loss, dietary modifications and insulin-sensitizing medications.

The use of anti-diabetic drugs in PCOS represents a novel use of these agents. The management of PCOS should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the insulin resistant patient with PCOS. This is not only important in the primary treatment of PCOS but in maintaining efficacy of drug therapy.