POLYCYSTIC OVARY SYNDROME (PCOS), INSULIN RESISTANCE (IR), & METFORMIN: LATEST DEVELOPMENTS

I. Lane Wong, M.D., F.A.C.O.G.
Board Certified, Reproductive Endocrinology and Infertility

Recently, there has been much compelling research involving Polycystic Ovary Syndrome (PCOS), highlighted by the evolving understanding of the association between PCOS and Insulin Resistance (IR) and the efficacy of metformin (Glucophage®) treatment. The goal of this article is to provide a practical review of PCOS, IR, and metformin.

What is PCOS?

Despite continuing research on its pathophysiology, PCOS remains a syndrome, a heterogeneous disorder, not a specific disease. As a syndrome, there is a group of symptoms and signs that are recognized to be associated with each other but are without an understood common cause. The usual symptoms and signs identified with PCOS are oligo or amenorrhea, infertility, hirsutism, obesity, polycystic ovaries, androgen excess, IR, and elevated LH / FSH ratio (1). PCOS is the most common endocrinopathy in women, occurring in about 5% of reproductive-aged women (2).

The most popular definition of PCOS is hyperandrogenic chronic oligo or anovulation. More specifically, PCOS is defined as unexplained hyperandrogenic chronic anovulation. Excluded by this definition of PCOS are known causes of hyperandrogenic chronic anovulation such as non-classic adrenal hyperplasia and rare androgen producing ovarian tumors (3). The definition of PCOS is evolving. The NIH sponsored a conference on PCOS in 1990 and 2001. Although both conferences affirmed the key importance of unexplained hyperandrogenism, the 2001 meeting de-emphasized anovulation, and placed more importance on the polycystic appearance of the ovaries on US (>8 follicles, 2-8 mm in diameter, increased ovarian stroma). US evidence of polycystic ovaries occurs in 16% of asymptomatic women (4).

Our studies of ovulatory women with isolated polycystic ovaries found they demonstrate a PCOS-like response to gonadotropin stimulation (that is, an exaggerated response) and subtle PCOS-like lab alterations (elevated androgens and decreased IGFBP1) (5,6). Because of findings such as these, the definition of PCOS is evolving from unexplained hyperandrogenic chronic anovulation to simply unexplained hyperandrogenism, often with polycystic ovaries, ovulatory disturbance, and IR.

How is PCOS diagnosed?

Unexplained hyperandrogenism is the key finding. Clinical evidence of androgen excess is provided by findings of hirsutism, androgenic alopecia, or acne. These findings may be muted in women with less skin sensitivity to androgens, e.g. Asian women with

PCOS. Lab evidence of hyperandrogenemia can often be provided by measurement of serum free or total testosterone, androstenedione, or dehydroepiandrosterone sulfate. However, because of limitations of commercially available tests, hyperandrogenemia may not be evident unless specialized immunoassays or bioassays are conducted (7). Exclusion of known causes of hyperandrogenism is usually simply accomplished by history and exam. With irregular menses, TSH and prolactin levels should be measured. With rapidly progressive or marked hyperandrogenism, less common conditions should be considered.

For example, non-classic adrenal hyperplasia due to 21-hydroxylase deficiency can be excluded by a 17-hydroxyprogesterone level less than 2 ng/mL and rare androgen producing ovarian tumors will often be detected by vaginal US (3). Furthermore, vaginal US will identify the classic polycystic ovarian morphology; although not mandatory for the diagnosis, it is corroboratory evidence of PCOS (1).

What is Insulin Resistance?

With PCOS defined as unexplained hyperandrogenism and chronic anovulation, about 40% of PCOS women will have IR (8). IR refers to a state in which for a given amount of insulin, there is a less than normal reduction of glucose. The pancreatic beta cells initially compensates for this resistance by producing excess amounts of insulin. If glucose levels are maintained within normal ranges, the person simply has IR with high insulin levels. If however, glucose levels are moderately high (fasting glucose $\geq$ 110 or $\geq$ 140 two hours after a 75-gram glucose load) the person has Impaired Glucose Tolerance (IGT). If glucose levels are very high (fasting glucose $\geq$ 126 or $\geq$ 200 two hours after a 75-gram glucose load) the person has type 2 diabetes.

With time, a person with IR has a tendency to progress from high insulin levels with normal glucose levels to abnormally high glucose levels, that is, IGT or type 2 diabetes. This is because beta cell function tends to deteriorate. When beta cells can no longer produce the excessive amounts of insulin needed in IR to control glucose levels, insulin levels fall allowing abnormally high glucose levels to develop, resulting initially in IGT, and ultimately, if left unchecked, type 2 diabetes.

How is Insulin Resistance related to PCOS?

The high insulin levels associated with IR stimulate the ovary to make excessive amounts of androgens. Additionally, high insulin levels decrease levels of SHBG, increasing the androgens potency. High insulin levels may also work at the level of the brain, causing increased LH secretion (which in turns stimulates more ovarian androgen production) and stimulating appetite. Increased LH secretion, high androgen levels, and obesity disrupt ovulation. These complex and interrelated effects lead to "unexplained hyperandrogenic chronic anovulation" that is, PCOS. This begs the question, what is "unexplained"? There seemingly is an explanation for the hyperandrogenic chronic anovulation, namely IR with high insulin levels. The answer is IR itself is unexplained. It too is a syndrome ("syndrome X"), a heterogeneous metabolic disorder without a known specific cause.
How is Insulin Resistance diagnosed?

Clinically, IR is suggested on exam by obesity (BMI >30 kg/m2), a central adipose distribution ('apple shaped' [waist-hip ratio >0.85] as opposed to 'pear shaped'), and acanthosis nigricans (raised, velvety, usually hyperpigmented, nuchal and axillary skin changes). Lab tests can provide unequivocal proof of IR with the diagnosis of IGT or type 2 diabetes by established criteria such as those of the WHO listed above. Prior to progression to IGT or type 2 diabetes, however, there isn't a universally agreed upon simple lab test to screen for IR.

In the research setting, detection of IR usually involves IV infusions, multiple blood draws, and complex analysis ("clamp technique"); it is clinically impractical. A pragmatic, clinical approach to the diagnosis of IR is to perform a 75 gram oral glucose tolerance test, measuring fasting and 2 hour glucose levels. By this approach, IGT or type 2 diabetes may be revealed, proving advanced insulin resistance. Short of this, IR may be suggested by an elevated fasting insulin level (>20 microU/mL), a reduced fasting glucose / insulin ratio (G/I <4.5), or an elevated 2 hour insulin level following a 75-gram glucose load (9). However, there aren't well-established criteria or studies to validate the use of these tests to diagnose IR. Also note, insulin levels are notoriously difficult to measure accurately and, of course, in the face of advanced progression, namely, IGT or type 2 diabetes, insulin levels will not be high because of B cell exhaustion.

IR is very common in the general population; its prevalence is dependent on screening method, age, and body weight. Overall, the prevalence of IR is 2-5 times higher than that of PCOS. Therefore, many women will have IR but not PCOS; conversely, some women with PCOS will not be insulin resistant. In a study of 254 women with PCOS, almost 40% had abnormal glucose tolerance (31% had IGT, 7.5% had previously undiagnosed type 2 diabetes). In the non-obese women with PCOS, 10% had IGT, 1.5% had type 2 diabetes; these rates are 3 times higher than the non-PCOS controls (7,8).

Besides IGT and Type 2 Diabetes, what other medical problems are associated with PCOS?

Because PCOS is associated with abnormal lipid profiles, especially elevated LDL, there is concern that there is an increased risk for cardiovascular events. Large, prospective studies have yet to be conducted to prove this. However, small cohort studies, using surrogate endpoints for cardiovascular disease are suggestive. For example, in one study the prevalence for subclinical atherosclerosis in PCOS women was 10 times higher, 7.2% compared to 0.7% in controls of similar age. This difference was detected only in women aged 45 years or older (10). Women with PCOS are at increased risk of developing endometrial neoplasia unless they have periodic menses resulting from progesterone administration, birth control pills, or induction of ovulation.

What is Metformin (Glucophage®)? Why has it become so popular?

Metformin was originally developed in 1957 and used worldwide before finally being introduced to the US in 1994. It is approved by the FDA for treatment of type 2 diabetes. Metformin is a biguanide oral antihyperglycemic. It has many actions, the main being suppression of endogenous glucose production by the liver. Among oral

antihyperglycemic medications it is unique, unlike the sulfonlyureas such as Diabinese® it does not cause hypoglycemia, weight gain, unfavorable alteration of lipids, nor increase insulin secretion. Unlike thiazolidinediones such as Avandia® it does not cause weight gain, fluid retention, or potential idiosyncratic hepatotoxicity. Instead, metformin improves the effectiveness of insulin while maintaining or even decreasing insulin levels. It decreases both basal and postprandial glucose levels, without the danger of hypoglycemia. Metformin promotes weight loss and favorable changes in the lipid profile. All of these effects are beneficial to women with type 2 diabetes. Metformin's unique properties have already established it as the initial medication of choice for type 2 diabetes treatment and produced many studies advocating other possible indications:

- Metformin may decrease the progression from IGT to type 2 diabetes. In a prospective RCT, 3,234 women with IGT were followed for an average of 2.8 years. With placebo treatment, 11% per year progressed to type 2 diabetes. With a weight loss and exercise program, 4.8% per year progressed (a 58% improvement vs. placebo). With metformin treatment, 7.8% per year progressed (a 31% improvement vs. placebo) (11). Weight loss and exercise remains the best hedge against developing IGT or type 2 diabetes. The usefulness of metformin treatment in women simply with PCOS to prevent the development of IGT or type 2 diabetes is unknown.
- In women with PCOS, three randomized, placebo controlled trials found metformin plus clomiphene to be more effective than clomiphene alone in ovulation induction. Metformin may also improve the quality of ovulation induced by recombinant FSH administration. Sustained metformin administration may establish regular menses in women with PCOS (12).
- Metformin may decrease the miscarriage risk associated with PCOS. These findings are preliminary, based on two small studies. PCOS is not associated with the most incessant forms of recurrent miscarriage. One small study found metformin may also decrease the incidence of gestational diabetes in PCOS women. The safety of metformin use in pregnancy has not been established (13,14).
- Preliminary studies of metformin's effectiveness as a treatment for hirsutism have been mixed.

Metformin is chemically related to phenformin, which was withdrawn from the US market in 1976 because of a high association with lactic acidosis. With normal metformin dosing and normal renal function, development of lactic acidosis is very rare. It is prudent to verify a normal serum creatinine level before starting metformin and to stop metformin treatment before conditions of relative renal compromise such as the administration of IV iodinated contrast agents and during fluid restriction. Cationic medications, such as cimetidine, compete with metformin for renal clearance thus increasing the risk of lactic acidosis. Other contraindications to metformin are liver dysfunction, excessive alcohol intake, and severe illness. The main side effects of metformin are GI: diarrhea, nausea. These effects can be mitigated by taking metformin with food and slowly building up to the target dosage of 1,500 to 2,000 mg total per day.

Summary:

• PCOS is a syndrome, defined by unexplained hyperandrogenism and associated ovulatory dysfunction. Although not essential to its definition, PCOS will usually be accompanied by polycystic ovaries, and in about half the women, IR (1,8).

• IR is suggested clinically by central obesity and acanthosis nigricans. IR is a given with IGT or Type 2 Diabetes. Because of its high prevalence in PCOS, a strong case can be made for all women with PCOS to undergo an OGTT to detect IGT and Type 2 Diabetes. Unfortunately, proven practical means to screen for less advanced forms of IR are not established. Elevated fasting insulin levels and decreased fasting glucose insulin ratios (G/I <4.5) are consistent with early IR, before beta cell exhaustion (8,9). With IGT or Type 2 Diabetes, the best intervention is weight loss and exercise. Metformin is generally the first choice among pharmacologic agents.

• For most women with PCOS trying to conceive, the first medication option to induce ovulation is still clomiphene. However, metformin is arguably the first choice in women with IGT and certainly in women with type 2 diabetes. The combination of metformin and clomiphene is effective. Weight loss and exercise promote ovulation.

• In women with PCOS not trying to conceive, menstrual irregularity is usually best treated with an estrogen-progestin contraceptive. In some women, it is possible that sustained metformin treatment may induce regular, ovulatory menstruation (12).

• In women with PCOS not trying to conceive, hirsutism treatment initially usually consists of an estrogen-progestin contraceptive, an anti-androgen such as spironolactone, and mechanical cosmetic treatment (15).

• Metformin is a very safe medication when used properly and given to healthy women. It is contraindicated in women with renal compromise, liver disease, and at risk for lactic acidosis. GI side effects are initially very common, but usually are not severe or sustained.

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