

Polycystic Ovary Syndrome (PCOS), Insulin Resistance (IR), & the Metabolic Syndrome: An Update

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Polycystic Ovary Syndrome (PCOS), Insulin Resistance (IR), Impaired Glucose Tolerance (IGT), Type 2 Diabetes, and the Metabolic Syndrome are common conditions, constantly in the news. How do these conditions affect fertility? How are they diagnosed, related, and treated?

What is Polycystic Ovary Syndrome (PCOS)? PCOS is a common endocrine disorder, occurring in about 5% of reproductive-aged women (1). PCOS is a **syndrome**, not a specific disease. In medicine, a syndrome is a group of symptoms and signs that are recognized to be associated with each other but are without an understood common cause as is known to diseases. In 2003, the American and European reproductive societies revised criteria for what symptoms and signs define PCOS (**Table 1**) (2).

Table 1. PCOS: New Diagnostic Criteria

At least 2 of the following 3 needed:

- Infrequent or No Ovulation (Chronic Anovulation).
- Excessive Androgens by physical exam or blood levels (Hyperandrogenism).
- Polycystic Ovaries.

AND Exclusion of known causes of the above.

PCOS is a syndrome consisting of the following triad:

- 1) Chronic Anovulation:** Infrequent or no ovulation resulting in **irregular or no periods**, and often **infertility** due to lack of ovulation.
- 2) Hyperandrogenism:** Excessive ‘male-type’ hormones (androgens) often causing excessive facial and body hair (**hirsutism**) and acne. If these signs are not present, lab evidence of Hyperandrogenism can be sought by measuring blood androgen levels (testosterone, dehydroepiandrosterone sulfate).
- 3) Polycystic Ovaries.** An ovary normally contains small fluid filled structures called cysts; many are “follicular cysts” which contain eggs. A Polycystic Ovary contains excessive number of cysts and is enlarged. (The ultrasound definition of a Polycystic Ovary is an ovary with twelve or more cysts, 2-9 mm in diameter and/or increased ovarian volume [>10 cc]. Ovarian volume [cc] can be estimated by multiplying length x width x thickness [cm] x 0.5.) Because Polycystic Ovaries can be created by any condition that inhibits ovulation, it should not be diagnosed while a woman is on birth control pills.

Traditionally, most American physicians have defined PCOS simply as unexplained Chronic Anovulation with Hyperandrogenism. Interestingly, our studies of regularly ovulating women with isolated polycystic ovaries found they demonstrate a PCOS-like, exaggerated response to stimulation and subtle PCOS-like lab alterations (3,4). It is these types of findings that support the recent inclusion of Polycystic Ovaries itself as a diagnostic criterion for the syndrome.

To qualify for the diagnosis of PCOS **known** causes of Chronic Anovulation, Hyperandrogenism, and Polycystic Ovaries are **excluded**. This can usually simply be accomplished by history and exam. However, **with irregular periods**, thyroid stimulating hormone and prolactin levels should be measured and excluded as causes of Chronic Anovulation. **With rapidly progressive or marked Hyperandrogenism**, less common conditions of excessive androgens 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 ultrasound (5).

What is Insulin Resistance (IR)?

With PCOS defined as unexplained hyperandrogenism and chronic anovulation, **about 40% of PCOS women will have IR (Figure 1)** (6). Insulin is made by the beta cells of the pancreas. Insulin's overall effect is the lowering of glucose levels. **IR refers to a state in which for a given amount of insulin, there is a less than normal reduction of glucose.** The beta cells initially compensate 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 the person has **Impaired Glucose Tolerance (IGT)**. If glucose levels are very high 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 (**Table 2**).

Table 2. Comparing Normal, States of Insulin Resistance (IGT, Type 2 Diabetes).		
<u>Diagnosis</u>	<u>Insulin Levels</u>	<u>OGTT (Oral Glucose Tolerance Test)</u> Glucose levels (mg/dL) Fasting & 2 hrs after 75gm Glu load
“Normal”	<u>Normal.</u>	<u>Normal.</u> Fasting: <110 and 2 hrs: <140
“Insulin Resistance (IR)”		
pre-IGT	<u>High</u> insulin levels are needed to control Glu levels.	<u>Normal still.</u>
with <u>IGT (Impaired Glucose Tolerance)</u>	Not as high. Beta cells ‘exhausting,’ can’t make enough insulin, Glu levels rise.	<u>High.</u> Fasting: 110-125 or 2 hrs: 140-199
with <u>Type 2 Diabetes</u>	Beta cells ‘exhausted,’ can’t make enough insulin, Glu levels rise higher.	<u>Very High.</u> Fasting: >125 or 2 hrs: >199

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 sex hormone binding globulin, increasing the androgens potency. High insulin levels may also work at the level of the brain, causing increased LH (luteinizing hormone) secretion (which in turns stimulates more ovarian androgen production) and appetite. Increased LH secretion, high androgen levels, and obesity disrupt ovulation. **These complex and inter-related effects lead to “unexplained hyperandrogenic chronic anovulation” that is, PCOS.** Insulin resistance thus can provide an explanation for hyperandrogenic chronic anovulation for some women. However, one clue leads to another question, as IR itself is unexplained. It too is part of a syndrome, the “**Metabolic Syndrome**,” also known as “Syndrome X,” and the “Syndrome of Insulin Resistance,” a diverse metabolic disorder without a known specific cause (**Table 3**) (2).

Table 3. The Metabolic Syndrome (Syndrome X)

3 or more risk factors for the diagnosis:

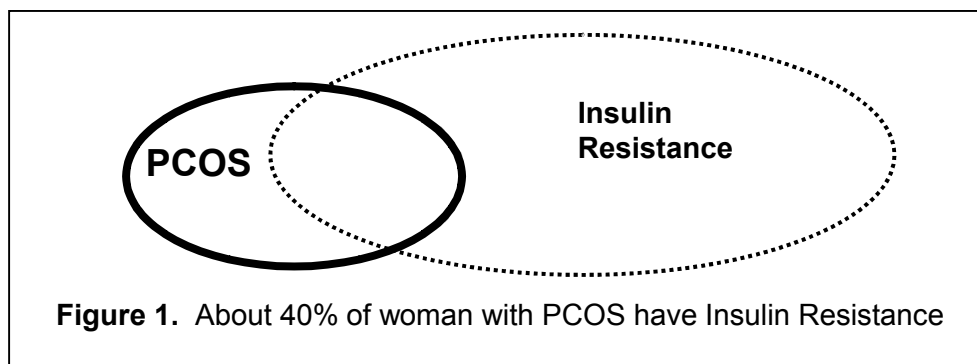
- Central Obesity (waist >35 inches)
- Triglycerides elevated (≥ 150 mg/dL)
- HDL Cholesterol low (< 50 mg/dL)
- Blood Pressure elevated (≥ 130 / ≥ 85 mm Hg)
- Impaired Glucose Tolerance (IGT)

How is Insulin Resistance diagnosed?

Clinically, IR is suggested on exam by central (waist >35 inches) obesity (BMI >30 kg/m²) and acanthosis nigricans (raised, velvety, usually hyperpigmented skin changes often at the back of the neck). **Lab tests can provide obvious clinical evidence of IR with the diagnosis of IGT or type 2 diabetes (Table 2).**

Prior to progression to IGT or type 2 diabetes, however, there isn't a universally agreed upon simple validated lab test to screen for IR. **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 (peak insulin level >100 microU/mL) (7). 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 (10-25%); 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 (Figure 1).** In a study of 254 women with PCOS, 31% had IGT, 7.5% had type 2 diabetes (6).



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

Because PCOS can be associated with abnormal lipid (cholesterol, triglyceride) profile, hypertension, and obesity (**Metabolic Syndrome - Table 3**), there is concern that woman with PCOS may be at increased risk for heart disease and strokes. Large, prospective studies have yet to be conducted to prove this. However, a small cohort study examining plaque formation in carotid arteries was suggestive (8). Women with PCOS are at increased risk of developing endometrial neoplasia (uterine cancer) unless they have periodic menstruation resulting from progesterone administration, birth control pills, or induction of ovulation.

What is Metformin (Glucophage®)?

Metformin is an oral medication approved by the FDA for treatment of type 2 diabetes. It has many actions, the main being suppression of endogenous glucose production by the liver. Metformin improves the effectiveness of insulin while maintaining or even decreasing insulin levels. It decreases fasting and after meal glucose levels usually without the danger of clinical hypoglycemia. Metformin promotes weight loss and favorable changes in the lipid profile. Metformin's many unique and beneficial properties have 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 trial, 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 metformin treatment, 7.8% per year progressed (a 31% improvement vs. placebo). **Weight loss and exercise treatment group did even better**, only 4.8% per year progressed (a 58% improvement vs. placebo) (9). It is unknown if metformin is helpful in preventing women simply with PCOS from developing IGT.
- In women with PCOS, three trials found metformin plus clomiphene to be more effective than clomiphene alone in inducing ovulation. Metformin may also improve the quality of ovulation induced by FSH stimulation. Sustained metformin administration may be able to establish regular ovulation and thus periods in women with PCOS (10). **A recent trial examining birth rates, not ovulation**

rates, however, found the birth rate with clomiphene alone and metformin with clomiphene, superior to the birth rate with administration of metformin alone (11).

- Metformin may decrease the possible miscarriage risk associated with PCOS. These findings are preliminary, based on small studies. Fortunately, PCOS is not associated with the most unrelenting forms of recurrent miscarriage. Although, the safety of metformin's use in pregnancy has not been fully established, its use during pregnancy may decrease the incidence of gestational diabetes in PCOS women (12, 13).

Metformin usage can be associated with **lactic acidosis** (a dangerous condition of lactic acid build up in the body). With standard metformin dosing and normal kidney function development of lactic acidosis is very rare. **Contraindications** to metformin are risk factors for lactic acidosis, renal compromise, severe illness, and liver dysfunction. The main **side effects** of metformin are GI: diarrhea, nausea. **These effects can be lessened 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 common syndrome, defined by unexplained Chronic Anovulation (infrequent or no ovulation / irregular periods), Hyperandrogenism (elevated male-type hormones) and Polycystic Ovaries. Almost half the women with PCOS will also have Insulin Resistance (Table 1, Figure 1).
- **Insulin Resistance** is a given with Impaired Glucose Tolerance or type 2 diabetes. IR is suggested clinically by central obesity & acanthosis nigricans. Women with PCOS, especially those obese or with irregular periods are recommended to have an Oral Glucose Tolerance Test to detect IGT and type 2 diabetes. Unfortunately, there isn't a universally agreed upon easy method of diagnosing IR prior to the development of IGT or type 2 diabetes (Table 2).
- **For most women with PCOS trying to conceive**, the first medication option to induce ovulation is 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, as is weight loss and exercise. FSH injections will essentially always be able to cause ovulation, however they are usually not first line medications because of cost and potential for overstimulation of the ovaries.
- **For more details, please refer to the Table "PCOS: More Details" after the references.**

(1) Carmina E, Lobo RA. J Clin Endocrinol Metab. 1999;84:1987.

(2) ESHRE/ASRM. Fertil Steril. 2004;81:19-25.

(3) Wong IL, Morris RS, Paulson RJ, Lobo RA, Sauer MV. Hum Reprod 1995;10:524-528.

(4) Carmina E, Wong IL, Chang L, Paulson RJ, Sauer MV, Stanczyk FZ, Lobo RA. Hum Reprod 1997;12:905-909.

- (5) Wong IL, Lobo RA. In Adashi EY, Rock JA, Rosenwaks Z (eds). Reproductive Endocrinology, Surgery, and Technology. Philadelphia, PA, USA: Lippincott-Raven Publishers, 1996:1571-1598.
- (6) Legro RS, Kunselman AR, Dodson WC, Dunaif A. J Clin Endocrinol Metab. 1999;84:165-169.
- (7) Legro RS, Finegood D, Dunaif A. J Clin Endocrinol Metab. 1998;83:2694-2698.
- (8) Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Arterioscler Thromb Vasc Biol. 2000;20:2414-2421.
- (9) Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. N Engl J Med. 2002;346:393-403.
- (10) Barbieri RL. Obstet Gynecol. 2003;101:785-793.
- (11) Legro RS, et al. N Engl J Med. 2007;356(6):551-66.
- (12) Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Hum Reprod. 2002;17:2858-2864.
- (13) Legro RS. Clin Obstet Gynecol. 2007 Mar;50(1):295-304.

PCOS: More Details

<u>Test</u>	<u>Indications for Test</u>	<u>Interpretation</u>
Testosterone	<p>Total Testosterone (and Free Testosterone) levels are often measured if:</p> <p>There aren't definitive clinical signs of hyperandrogenism and lab evidence of hyperandrogenism is sought (e.g. Asian women with PCOS are less likely to be hirsute because of less skin sensitivity to androgens)</p> <p>OR</p> <p>Because the onset, progression or degree of hyperandrogenism causes concern of an androgen producing tumor.</p>	<ul style="list-style-type: none"> • Testosterone is considered the single best marker of androgen production from the Ovary. Note however that, the Adrenal gland contributes equally to T production. • With PCOS, generally T levels are <2x upper limits of normal. Hirsutism is gradually progressive and there are no signs of virilization. • Ovarian or Adrenal androgen producing tumors are very rare (5). They can be associated with sudden onset and rapidly progressive hirsutism, and virilization (loss of female habitus, bitemporal balding, clitoromegaly, etc). T levels can be very elevated, $\geq 2\frac{1}{2}x$ upper limits of normal.
DHEAS	<p>Dehydroepiandrosterone sulfate (DHEAS) levels are measured for the same reasons as indicated with testosterone.</p>	<ul style="list-style-type: none"> • DHEAS is virtually exclusively derived from adrenal production and thus is a good marker of adrenal androgen production. • PCOS DHEAS levels are usually <1.5x upper limits of normal. • Adrenal androgen producing tumor are very rare (5). They can cause DHEAS levels $\geq 2\frac{1}{2}x$ upper limits of normal. The adrenal tumors can also cause greatly elevated testosterone levels.
17-hydroxyprogesterone	<p>17-hydroxyprogesterone level is measured if non-classic adrenal hyperplasia (NCAH) (also</p>	<ul style="list-style-type: none"> • 17-hydroxyprogesterone should be measured in the morning (~08:00 AM), not

known as late onset adrenal hyperplasia) is a concern. NCAH is caused by a partial deficiency in the 21-hydroxylase enzyme activity. It is much more prevalent in women of certain ethnic backgrounds, e.g. Eastern European Jewish and Hispanic women.

NCAH should also be considered in women with a strong family history of androgen excess, high serum levels of androgens, or particularly progressive or marked clinical signs of hyperandrogenism

in the luteal phase. (Corpus lutea secrete 17-hydroxyprogesterone. Thus, levels normally rise in the luteal phase of the menstrual cycle. Women with NCAH will generally not be spontaneously ovulating.)

- A 17-hydroxyprogesterone level >200 ng/dL is generally considered a positive screen. Cortrosyn stimulation test is usually performed for confirmation of the diagnosis of NCAH.
- FSH levels are usually normal with PCOS. (In contrast, with premature ovarian dysfunction or menopause, FSH levels are elevated. Another cause of ovulation disruption is hypothalamic / stress, often FSH levels are low in this clinical situation.)
- LH is often relatively elevated in relationship to FSH in PCOS (LH/FSH > 2.5).

FSH, LH

FSH & LH levels are often checked if a woman is not ovulating or not ovulating regularly.

Prolactin

A serum prolactin level should be checked on all women with ovulatory dysfunction. Hyperprolactinemia, e.g. from a pituitary microadenoma, can cause oligoovulation and mild hirsutism.

Note: Up to 1/3 of women with PCOS will have very mildly elevated prolactin levels (<< 2x normal). Speculated cause is the relative hyperestrogenic state of PCOS, which increases prolactin production.

TSH

Thyroid stimulating hormone (third generation, high sensitivity) should be measured in all women with ovulatory dysfunction.

Both hyper and hypothyroidism can cause oligoovulation.

Urinary Free Cortisol

A test such as an Urinary Free Cortisol level should be obtained if clinical signs of the extremely rare Cushing's Syndrome are present. These signs include central obesity, wasting of the extremities, moon facies, facial plethora, supraclavicular adipose deposition, violaceous striae, hypertension.

One of the best screening test for excessive production of cortisol is a 24 hour collection of urine to determine the level of free cortisol (and creatinine). In most labs a level <100 mcg/day is normal. The screen is positive if >300 mcg/day.

Body Mass Index (BMI)

Preferred method of defining obesity.

BMI = weight in pounds divided by the square of height in inches, all of this multiplied by 703.

- BMI = 25-29.9 = overweight
- BMI = > 30 = obesity
- Average energy expenditure for women is 2,200 Kcal per day. A deficit of 500 to 1,000 Kcal per day will result in a weight loss of 1-2 pounds per week.

Insulin Resistance

See above Article, Table 2.

Oral Glucose Tolerance Test.

See above Article, Table 2.

If the OGTT is abnormal, and criteria are met (as defined in Table 2) for Impaired Glucose Tolerance or Type 2 Diabetes – **by definition Insulin Resistance is present.**

If the OGTT is normal, Insulin Resistance can still be present but is not at an advanced stage. There isn't an agreed upon, clinically practical,

simple way to diagnose IR in this situation. Nonetheless, **Insulin Resistance is suggested by:**

- Elevated Insulin levels in the face of normal Glucose levels. Namely: Elevated Fasting Insulin level (>20 microU/mL), Reduced Fasting Glucose / Insulin ratio (G/I <4.5), or an Elevated 2 hour Insulin level following a 75-gram Glucose load (peak insulin level >100 microU/mL) (7). Note: Insulin levels are notoriously difficult to measure accurately.
- Waist > 35 inches. (Waist/Hip >0.85.)
- Obesity – see BMI above.
- Acanthosis Nigricans (raised, velvety, usually hyperpigmented skin changes often at the back of the neck).
- An abnormally elevated level strongly suggests Impaired Glucose Tolerance or Type 2 Diabetes.
- It is important to control glucose levels prior to conception. Elevated glucose levels are teratogenic - the more abnormally elevated the Hemoglobin A1c levels are, the higher the risk of birth defects. Therefore, in diabetics, glucose levels should be controlled & the Hemoglobin A1c essentially normal before trying to conceive.

Hemoglobin A1c

An easy way to generally check Glucose levels over the past 3 months. Does not require fasting.