



# CONCEPTION

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Center for Advanced Reproduction, Endocrinology & Surgery, PA

Gordon B. Kuttner, MD, FACOG, FACS

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Welcome to the inaugural issue of **CONCEPTION** sponsored by **The Center for Advanced Reproduction, Endocrinology & Surgery (CARES)**. The objective of our newsletter is to provide health care professionals, caring for couples suffering from infertility, with current information on diagnosis and treatment. As a practicing, board certified, reproductive endocrinologist located in the Arboretum area, I am dedicated to staying abreast of the latest medical developments.

I will provide you with a synopsis of important concepts, breakthroughs and new and improved therapies that are relevant to the practice of fertility and reproductive endocrinology. Articles will address pathophysiology to assist in understanding the disease process, logical treatments, and practical information that you can use in your discussions with and management of patients. In doing this, I can serve my colleagues as a subspecialist consultant and patients as a primary care reproductive endocrinologist.

In this print issue, I discuss insulin resistance, its relationship to fertility and appropriate diagnosis and treatment options. I will focus on the use of metformin to restore spontaneous menstrual cycles, in ovulation induction with clomiphene citrate and gonadotropins, IVF, and as potential treatment for gestational diabetes and spontaneous abortions. Due to space constraints, an expanded, in-depth review of insulin resistance including its long and short-term implications for overall health, dosing protocols, and additional off-label uses is located at [www.caresmed.com](http://www.caresmed.com) under Newsletter- **CONCEPTION**.

Since the establishment of **CARES**, I have appreciated the support from the greater Charlotte medical community. Referring health care practitioners have commented that they, and their patients, derive benefit from collaborating as part of a team optimizing individual patient care. In addition, patients appreciate receiving the highest quality of reproductive medicine in a compassionate, relaxed, state-of-the-art, and conveniently located, private office setting.

Your feedback, and that of your patients', is appreciated. We are always receptive to suggestions that will improve patient care and health provider relationships. Please contact me at [gkuttner@caresmed.com](mailto:gkuttner@caresmed.com) or 704-542-6006 to make comments, suggest newsletter topics, or if you would like to discuss the management of a challenging clinical case.

Thank you for your support and I will continue to do my best to serve you and your patients as a resource for reproductive endocrinology and fertility issues. I look forward to meeting you personally.

**CARES' philosophy and mission is to empower patients through education and clear communication, and to provide them with excellent reproductive health care, outstanding highly individualized service, and the benefits of the latest applied medical research. We are committed to quality, integrity, privacy, collaboration and teamwork. We maintain a strong commitment to working closely with our referring providers to provide integrated patient care.**

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## Insulin Resistance: Effects in Women

**History** In the 1930s, Stein and Leventhal first described a complex of symptoms associated with ovulation dysfunction and hyperandrogenism (clinical hirsutism or elevated testosterone and androstenedione levels) now known as polycystic ovarian syndrome (PCOS). PCOS affects approximately 5 to 7% of reproductive age women. Research has revealed that these clinical manifestations are due to persistent ovulation dysfunction resulting from numerous causes that now include insulin resistance, hyperinsulinemia, and hyperandrogenism.

**PCOS Genetic Link** Clinicians have seen familial patterns of PCOS suggesting a genetic component. Research has demonstrated a possible X-linked dominant transmission and autosomal dominant mode of inheritance. A germline mutation in the insulin receptor gene has been implicated as an etiology of insulin resistance in some cases. Over the last several years, the association between insulin resistance and PCOS has become more evident and is one of the most important relationships uncovered regarding this condition affecting both obese and thin women.

**Insulin Resistance** Insulin resistance (IR) is defined as a reduced glucose response to a given amount of insulin. There are several clinical and laboratory criteria clinicians use to define insulin resistance, but no one is accepted by all. Such criteria include the BMI  $> 27 \text{ kg/M}^2$ , a waist/hip ratio  $> 0.85$ , the presence of acanthosis nigricans, an elevated fasting insulin concentration, and decreased glucose/insulin ratio. Resistance to insulin-stimulated glucose uptake is relatively common, often referred to as Syndrome X. Not all women who are insulin resistant are hyperandrogenic or have impaired glucose tolerance. There are several mechanisms described for insulin resistance: peripheral target tissue resistance, decreased hepatic clearance, and increased pancreatic sensitivity. Hyperinsulinemia contributes to the increased risk of cardiovascular disease by means of a direct atherogenic action and indirectly by adversely affecting the lipoprotein profile. There is a direct relationship between hyperinsulinemia and hypertension although not evidenced until the menopausal years. In addition, there is also an association with increased production of plasminogen activator inhibitor type 1 (PIA-1) that has been linked to increased risk of coronary and vascular disease due to the decrease in the fibrinolytic activity.

Overweight is defined as having a BMI 25-30  $\text{kg/M}^2$ , obesity is defined as having a BMI  $> 30 \text{ kg/M}^2$ . Ovulation dysfunction occurs with a BMI  $> 25 \text{ kg/M}^2$ . Generally, all obese women are insulin resistant, as are most overweight women. Obese, anovulatory women with hyperandrogenism have a characteristic distribution of body fat known as android (central body) obesity, similar to that seen in older men with a pear shaped body habitus. This fat distribution is associated with hyperinsulinemia, impaired glucose tolerance, diabetes mellitus, and an increase in androgen production resulting in decreased levels of sex hormone-binding globulin (SHBG) and increased levels of free testosterone and estradiol. Android obesity is also associated with cardiovascular risk factors.

Research supports hyperinsulinemia produces hyperandrogenism in PCOS patients: (1) the administration of insulin to women with PCOS increases androgen levels, (2) the administration of glucose to hyperandrogenic women increases levels of both insulin and androgens, (3) weight loss decreases levels of both insulin and androgens, and increases the level of insulin-like growth factor binding protein-1 (IGFBP-1), (4) insulin stimulates theca cell androgen production in vitro, (5) reduction of insulin levels reduces androgen levels in women with PCOS, but not in normal women, and (6) after normalization of androgens with GnRH agonist treatment, the hyperinsulin response to glucose tolerance testing remains abnormal in obese woman with PCOS.

Hyperinsulinemia produces hyperandrogenism when there are a reduced number of functional insulin receptors or when blocked. Circulating insulin then binds to IGF receptors, which are structurally similar to the insulin receptor and results in androgens produced by theca cells. In addition, hyperinsulinemia inhibits hepatic synthesis of SHBG and hepatic production of IGFBP-1. Lower levels of SHBG allows for increased circulating levels of androgens and estrogens. Lower levels of circulating IGFBP-1 increases IGF activity resulting in increased theca cell androgen production. Lastly, insulin may directly increase the LH secretion in obese, anovulatory women. All of these events propagate ovulation dysfunction.

**Clinical Consequences** By the age of 40, up to 40% of PCOS patients develop impaired glucose tolerance or clinical diabetes. During the reproductive years, these women are more likely to experience, infertility, endometrial cancer, spontaneous abortions, and develop gestational diabetes. Those who develop gestational diabetes are at increased risk of developing hyperandrogenism and hyperinsulinemia later in life.

**Diagnosis of Hyperinsulinemia** Both thin and obese women with ovulatory dysfunction, hyperandrogenism and polycystic ovaries can be hyperinsulinemic. It is more common and severe in obese women. Not all hyperandrogenic women (thin and obese) have elevated insulin levels. Thin women with hyperinsulinemia are less likely than obese women to develop early-onset diabetes mellitus. Ideally, all obese patients should be tested for hyperinsulinemia. One criterion is to test women with a waist circumference > 35 inches, which is predictive of abnormal endocrine and metabolic function and associated with an increased risk of cardiovascular disease. Adolescents who present with premature adrenarche and those with early ovulatory dysfunction should also be tested. Many of these adolescents will develop all of the long and short-term complications associated with chronic anovulation.

**CARES** obtains a fasting glucose (FG) and fasting insulin (FI) on thin and obese women with ovulation dysfunction regardless of clinical manifestations of hyperandrogenism. If the ratio of FG/FI < 4.5, the patient is diagnosed with insulin resistance. Those women who meet this criterion are offered metformin treatment. Concurrently, we order a 2-hour glucose level after 75 g glucose load. Normal glucose tolerance is < 140 mg/dl, impaired 140-199 mg/dl, and non insulin-dependent diabetes mellitus > 200 mg/dl. Those women who demonstrate impaired glucose tolerance or insulin-dependent diabetes mellitus are referred to their primary care providers.

*Both thin and obese women can be hyperinsulinemic. CARES obtains FG and FI levels on all women with ovulation dysfunction regardless of clinical manifestations of hyperandrogenism. If the ratio of FG/FI < 4.5, the patient is diagnosed with insulin resistance and offered metformin.*

**Treatment** If hyperinsulinemia, due to insulin resistance, truly produces the clinical short and long-term sequelae of PCOS, then treatments that decrease insulin resistance should also decrease hyperandrogenism and restore cyclic menses, alleviating the major cause of infertility associated with PCOS. Treatment objectives are (1) reduce the production and circulating levels of androgens, (2) avoid the long-term effects of hyperinsulinemia, the risk of cardiovascular disease and diabetes mellitus, (3) protect the endometrium from the effect of unopposed estrogen, (4) encourage lifestyle changes to achieve normal body weight, (5) induction of ovulation to achieve pregnancy, (6) decrease spontaneous abortion rates, and (7) decrease gestational diabetes and its resultant effects.

**Lifestyle Modification** with weight loss is the best therapy. Weight reduction, improved nutrition, and exercise are behavioral modifications that should be encouraged as first-line therapy for obese PCOS patients. If diet and exercise fail, then medications may be introduced to improve peripheral insulin sensitivity and achieve a reduction in insulin secretion. Some of the oral insulin sensitizing medications approved by the FDA for the treatment of type II diabetes are metformin (Glucophage) and thiazolidinediones such as rosiglitazone (Avandia) and pioglitazone (Actos). Thiazolidinediones are briefly discussed in the expanded web version of this article.

**Metformin** reduces insulin resistance of peripheral tissue and allows muscle and adipose cells to utilize glucose at normal insulin levels. The drug improves insulin sensitivity by reducing intestinal absorption of glucose and significantly decreases hepatic glucose production, without causing hypoglycemia in either normal or patients with type II diabetes. Medical treatment with 500 mg t.i.d. or 850 mg b.i.d. reduces hyperinsulinemia, basal and stimulated LH levels, free testosterone concentrations, and PAI-1 levels in obese PCO patients. Metformin is rapidly absorbed from the small intestine with peak plasma levels occurring two hours after ingestion unless taken with food, which delays both. The plasma half-life is approximately 6 hours and is cleared by the renal system. Metformin is available in 500 mg, 850 mg, and 1000 mg tablets. An extended release form is available in 500 mg tablets. Clinical results are usually observed at doses between 1500 mg and 2550 mg daily. Resumption of spontaneous ovulation is dependent on the length of treatment with metformin. Most individuals require 4-6 months of treatment before ovulatory menses occur. Dosing schedules and side effects are discussed in the expanded web text.

**Metformin and Ovulation Induction with Clomiphene Citrate** There is overwhelming evidence from at least three well performed, randomized, controlled trials and several cohort studies indicating that when taken with clomiphene citrate, metformin enhances the probability of ovulation and pregnancy. There is controversy over the mechanism of action. Some suggest that these

outcomes were due to the weight loss that results when using metformin. Only a few studies have shown that metformin has no or minimal effect on insulin resistance and these studies were in morbidly obese PCO patients or when there was no weight loss. Numerous studies have shown that metformin is effective in both obese and thin women correcting insulin metabolism, endocrine parameters or both. Some studies on the effects of metformin have revealed positive trends without achieving statistical significances. This may imply that there are subsets of PCOS patients that may not benefit from metformin use.

**Metformin and Ovulation Induction with Gonadotropins and IVF** Metformin also improves clomiphene resistant anovulation in women treated with follicle-stimulating hormone. Use of metformin significantly reduced the rate of cycle cancellation and ovarian hyperstimulation syndrome in comparison to gonadotropins alone. Research has shown PCOS patients undergoing IVF develop a greater number of poor quality oocytes demonstrated by lower fertilization and pregnancy rates probably due to higher levels of intrafollicular androgens. In one prospective study, patients undergoing IVF treated with FSH and metformin had a significant increase in the number of mature oocytes retrieved, fertilization rates, and number of embryos produced. Insulin sensitizing medications have no risk of causing multiple gestations.

**Metformin and Pregnancy** Use of Metformin (FDA pregnancy category B) has not been linked to birth defects in animals or humans. Metformin has been used off-label to achieve pregnancy and throughout the first trimester to reduce the risk of spontaneous abortions. Although Metformin is not approved for use during pregnancy, it is being used more commonly off-label through the first trimester since it has been postulated, but not proven by randomized prospective trials, that its use may reduce the risk of early pregnancy miscarriages and reduce the risk of gestational diabetes with its sequelae.

**Metformin and Weight Loss** Metformin has been shown in clinical trials to have equal or superior results in comparison to low-calorie diets or to FDA approved weight loss medications.

**Summary** Through clinical observation, diagnostic testing, and implementing lifestyle and medical therapy, reproductive health care providers may be able to have a short-term and long-term impact on the lives of thin and obese women who are diagnosed with ovarian dysfunction, hyperinsulinemia, insulin resistance and hyperandrogenemia, commonly known as polycystic ovarian syndrome.

**An expanded, in-depth review of this subject and references can be found at [www.caresmed.com](http://www.caresmed.com) under Newsletter-Conception**

*Refer to the manufacture's product information regarding FDA approved indications, risks, benefits, dosages, and side effects.*



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***Address Correction Requested***

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