Polycystic Ovary Syndrome...
Treatment with Insulin Lowering Medications

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INTRODUCTION:
Polycystic ovary syndrome is characterized by anovulation *(irregular or absent menstrual periods)* and hyperandrogenism *(elevated serum testosterone and androstenedione)*. Patients with this syndrome may complain of abnormal bleeding, infertility, obesity, excess hair growth, hair loss and acne. In addition to the clinical and hormonal changes associated with this condition, vaginal ultrasound shows enlarged ovaries with an increased number of small (6-10mm) follicles around the periphery *(Polycystic Appearing Ovaries or PAO)*. While ultrasound reveals that polycystic appearing ovaries are commonly seen in up to 20% of women in the reproductive age range, **P**oly**C**ystic **O**vary **S**yndrome (PCOS) is a estimated to affect about half as many or approximately 6-10% of women. The condition appears to have a genetic component and those effected often have both male and female relatives with adult-onset diabetes, obesity, elevated blood triglycerides, high blood pressure and female relatives with infertility, hirsutism and menstrual problems.

HYPERINSULIN & PCOS?
As of yet, we do not understand why one woman who demonstrates polycystic appearing ovaries on ultrasound has regular menstrual cycles and no signs of excess androgens while another develops PCOS. One of the major biochemical features of polycystic ovary syndrome is insulin resistance accompanied by compensatory **hyperinsulinemia** *(elevated fasting blood insulin levels)*. There is increasing data that hyperinsulinemia produces the hyperandrogenism of polycystic ovary syndrome by increasing ovarian androgen production, particularly testosterone and androstenedione and by decreasing the serum sex hormone binding globulin concentration. The high levels of androgenic hormones interfere with the pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea, and infertility. Hyperinsulinemia has also been associated high blood pressure and increased clot formation and appears to be a major risk factor for the development of heart disease, stroke and type II diabetes.

DIAGNOSIS
There is little agreement when it comes to how PCOS is diagnosed. Most physicians will consider this diagnosis after making sure you do not have other conditions such as Cushing's disease *(overactive adrenal gland)*, thyroid problems, congenital adrenal hyperplasia or increased prolactin production by the pituitary gland. TSH, 17-hydroxyprogesterone, prolactin and a dexamethasone suppression test may be advisable. After reviewing your medical history, your physicians will determine which tests are necessary. If you have irregular or absent menstrual periods, clues from the physical exam will be considered next. Your height and weight will be noted along with any increase facial or body hair or loss of scalp hair, acne and acanthosis nigricans *(a discoloration of the skin under the arms, breasts and in the groin)*. Elevated androgen levels *(male hormones)* androstenedione, DHEAS or testosterone confirm the diagnosis. A fasting insulin and glucose level will be obtained. Many physicians tell their patients that insulin values are normal, when in fact the value indicates that insulin may be playing a role in stimulating the development of PCOS. Most labs report levels less than 25-30 miu/ml as normal, while in fact, levels over 10miu/ml on a fasting blood sample suggests that PCOS may be related to hyperinsulinism. As women with polycystic ovary syndrome may be a greater risk for other medical conditions, testing for blood lipids, diabetes and PAI-1 *(a blood factor that promotes abnormal clotting)*.

NEWER METHODS OF TREATMENT
Traditional treatments have been difficult, expensive and have limited success when used alone. Infertility treatments include weight loss diets, ovulation medications *(clomiphene, follistim, Gonal-F)*, ovarian drilling surgery and IVF. Other symptoms have been managed by anti-androgen medication *(birth control pills, spironolactone, flutamide or finasteride)*.

Ovarian drilling can be performed at the time of laparoscopy. A laser fibre or electrosurgical needle is used to puncture the ovary 10-12 times. This treatment results in a dramatic lowering of male hormones within

days. Studies have shown that up to 80% will benefit from such treatment. Many who failed to ovulate with clomiphene or metformin therapy will respond when rechallenged with these medications after ovarian drilling. Interestingly, women in these studies who are smokers, rarely responded to the drilling procedure. Side effects are rare, but may result in adhesion formation or ovarian failure if the procedure is performed by an inexperienced surgeon.

But recently promising new treatment options have become available. Drs. Velazquez, Nestler and Dunaif have shown that lowering serum insulin concentrations with metformin *(Glucophage 1500 mg a day)* or troglitazone *(troglitazone, Rezulin has recently been withdrawn from the market because of lifethreatening side effects)* ameliorates hyperandrogenism, by reduction of ovarian enzyme activity that results in male hormone production.

For women in the reproductive age range, polycystic ovary syndrome is a serious, common cause of infertility, because of the endocrine abnormalities which accompany elevated insulin levels. There is increasing evidence that this endocrine abnormality can be reversed by treatment with widely available standard medications which are leading medicines used in this country for the treatment of adult onset diabetes, metformin *(Glucophage 500 or 850 mg three times per day or 1000mg twice daily with meals)*, pioglitazone *(Actos 15-30 mg once a day)*, rosiglitazone *(Avandia 4-8 mg once daily)* or a combination of these medications. These medications have been shown to reverse the endocrine abnormalities seen with polycystic ovary syndrome within two or three months. They can result in decreased hair loss, diminished facial and body hair growth, normalization of elevated blood pressure, regulation or menses, weight loss and normal fertility. We have seen pregnancies result in less than two months in woman who conceived in their very first ovulatory menstrual cycle. By six months over 90% of women treated with insulin-lowering agents will resume regular menses.

The medical literature suggests that the endocrinopathy in most patients with polycystic ovary syndrome can be resolved with insulin lowering therapy. This is clinically very important because the therapy reduces hirsutism, obesity, blood pressure, triglyceride levels, elevated blood clotting factors and facilitates reestablishment of the normal pituitaryovarian cycle, thus often allowing resumption of normal ovulatory cycles and pregnancy. We know the polycystic ovary disease is associated with increased risk of heart attack and stroke because of the associated heart attack and stroke risk factors, hypertension, obesity, hyperandrogenism, hypertriglyceridemia, and these are to a large degree resolved by therapy with these medications.

ARE THESE MEDICATIONS SAFE?

Side effects are rare. Although metformin, rosiglitazone and troglitazone lower elevated blood sugar levels in diabetics, when given to nondiabetic patients, they only lower insulin levels. Blood sugar levels will not change. In fact, episodes of "hypoglycemic attacks" appear to be reduced.

METFORMIN (Glucophage):

When first starting this medication, people will often experience upset stomach or diarrhea which usually resolves after the first week. This side effect can be minimized by taking metformin with a meal and starting with a low dose. I recommend that our patients start with one 500 mg pill daily the first week and increase to twice a day during the second week. If after the second week GI side effects are minimal, the dose is increased to 850 mg twice daily. Patients with reduced renal function (creatinine >1.5 or creatinine clearance <60%) are at a higher risk for a rare side effect of metformin therapy called lactic acidosis, and the drug should be given cautiously, if at all, to such patients. Patients taking metformin should notify their physician and discontinue the medication:

- 48 hours before surgery
- 48 hours before an IVP Xray study or other Xrays where an intravenous dye is administered
- If you experience shortness of breath, severe muscle weakness or chest pain
- If you use alcohol excessively

TROGLITAZONE, *(Rezulin)* PIOGLITAZONE, *(Actos)*, ROSIGLITAZONE, *(Avandia)*:
These medications belong to a class of medications called PPAR gamma agonists. They enhance the ability of smooth muscle to metabolize sugar, thereby reducing insulin resistance.

The FDA has recently reviewed the safety of troglitazone *(and reports that 35 patients out of approximately 1.5 million have either died or required liver transplant.)* Therefore Rezulin has been removed from the market.

As the new alternatives to troglitazone, *(Rezulin)*, Rosiglitaone *(Avandia)* and pioglitazone *(Actos)* are metabolized by different liver enzymes experience has shown that these medications appear to pose less risk of hepatotoxicity.

HOW DO WE MONITOR THERAPY?
BBT charts are monitored and reviewed to determine if you are ovulating. With metformin, you will be asked to return three months after initiating therapy. If you have ovulated, therapy may be continued another three months to see if you will conceive. Women taking rosiglitazone or pioglitazone will be seen at two month intervals for monitoring liver function tests *(ALT)*. BBT charts will be reviewed after four months. Re-evaluation will include measurements of lab tests that were abnormal at the initial evaluation. C-peptide levels, a measure of insulin secretion, may also be tested. If the laboratory studies are still abnormal, metformin may be increased up to 850 mg three times daily or rosiglitazone may be added. If the laboratory studies are normal but ovulation has not occured, a repeat trial of clomiphene may be considered. We have seen that women who were unable to ovulate on up to 250 mg ovulate when 50 mg of clomiphene is used in conjunction with metformin or PPARgamma therapy.