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, PolyCystic Ovary Syndrome (PCOS) is 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.

What Causes 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 resistance to insulin 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.

Newer Methods of Treatment
Traditional treatments have been difficult, expensive and have limited success. Infertility treatments include weight loss diets, ovulation medications, ovarian drilling surgery and IVF. Other symptoms have been managed by anti-androgen medication (birth control pills, spironolactone, flutamide or finasteride)

But recently two 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 (Rezulin 400 mg a day) 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 with meals) or troglitazone (Rezulin 400 mg once a day). 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.

The medical literature suggests that the endocrinopathy in most patients with polycystic ovary syndrome can be resolved with metformin or troglitazone therapy. This is clinically very important because the therapy reduces hirsutism, obesity, blood pressure, triglyceride levels, and facilitates reestablishment of the normal pituitary-ovarian 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 metformin or troglitazone therapy.

**Are These Medications Safe?**

Side effects are rare. Fortunately, when given to non-diabetic patients, neither metformin or troglitazone while both appear to be very safe. In the first week of taking the medication, people will often experience upset stomach or diarrhea which usually resolves after the first week. For those on metformin, this side effect can be minimized by starting with one pill daily the first week and increasing to twice a day during the second week. 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.

While safety during pregnancy has not yet been established, three patients who continued on metformin during their entire pregnancy and one who remained on troglitazone have delivered normal babies. Dr. Glueck, Nestler, and I have all had patients who have conceived using metformin and all resulting babies were normal. These drugs are considered class B meaning that insufficient human data is available but no credible animal data suggests a teratogenic risk. Although to the best of our present knowledge the risk of birth defects would be small, it must be noted that maternal diabetes has been associated with an increased risk of birth defects and the underlying elevated insulin levels may lead to birth defects if not corrected. I feel the most prudent policy is to avoid the use of the medications during pregnancy until more data is available. Therefore, we ask all patients on these medications to monitor their basal body temperatures if pregnancy is a possibility. When the temperature remains elevated for more than 16 days, pregnancy is likely and a home pregnancy test should be performed. If positive, the medication is discontinued. If negative the BBT chart is reviewed by the physician or nurse to determine the appropriate course to follow.

**References:**

**Bibliography:**

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