PCOS and Insulin-Sensitizers

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Polycystic Ovarian Syndrome (PCOS)

Common symptoms associated with this condition include irregular menstrual cycles, excessive hair growth, obesity, acne, and hair loss. The menstrual irregularities are associated with infrequent or absent ovulation, which may lead to infertility.[1] The current criteria for diagnosis of PCOS is high levels of androgens (male hormones), particularly testosterone, and ovulatory irregularity that is not related to another disorder. Women with PCOS often have ovaries with many small cysts (polycystic ovaries) found on ultrasound exam. Although this finding is not necessary for diagnosis of PCOS it typically helps the doctor confirm the diagnosis. Besides these features, researchers have recently discovered that many women with PCOS have insulin resistance, or the inability of the body to properly use the sugar-regulating hormone, insulin.[2] -Anna

The Normal Ovulatory Cycle

In order to understand the role of insulin in PCOS and how it is treated with insulin-sensitizing medications it is necessary to briefly review the usual hormonal events that lead to successful ovulation. Normally, estrogen levels reach their lowest point when a woman is menstruating. At the same time LH (leutinizing hormone) and FSH (follicle stimulating hormone) levels begin to rise and encourage the development of an ovarian follicle, which contains the egg. The mature follicle produces androgens, which are released into the circulation. Some of these androgens will be bound to a protein in the bloodstream known as sex-hormone binding globulin (SHBG). These bound androgens have less of an effect on the body and are said to be inactive. The unbound or free androgens are active and may be converted in the body's fat tissue to estrogen. This process causes the level of estrogen to increase further, which initially causes a decrease LH and FSH. However, as estrogen continues to rise it eventually causes a surge in the production of LH, which causes the egg to be released from the follicle, otherwise known as ovulation.[3]

Insulin and PCOS

Recent studies indicate that insulin (the hormone responsible for the control of blood sugar) also plays a part in ovulation. Insulin causes LH and androgen levels to rise while causing the amount of SHBG to decrease. Too much insulin in the blood (hyperinsulinemia) over time can exaggerate these effects and lead to excessively high levels of LH and androgens along with low levels of SHBG.[4] Overall, this causes an increase in the amount of free androgens in the body, which is responsible for the excess hair growth, acne, weight gain and some other conditions associated with PCOS. Androgens can also have a local effect on the ovaries causing follicle atresia or abnormal development of the follicle. The conversion of these excess androgens into estrogen in the fat tissue can lead to elevated estrogen levels. High estrogen over a long period of time is responsible for the inability to ovulate and subsequent infertility.[5]

Hyperinsulinemia occurs when the cells of the body are insulin resistant or unable to properly use insulin. In a patient with PCOS, the body tries to solve this problem by producing more insulin. To prevent the body from over-producing insulin, it is necessary to make the cells more sensitive to it. Once, the production of insulin is slowed down, the blood levels of insulin will return to normal. Correcting these excessive levels of insulin may result in a decrease in the production of androgens followed by a reduction in PCOS symptoms, including a return to fertility.[6]

Insulin-sensitizing therapy

There are currently several medications available that increase insulin sensitivity. They are typically prescribed for patients with non-insulin dependent diabetes mellitus (Type 2 diabetes), however they also show promise for women with PCOS. See the chart below for medication details.

Insulin-sensitizing medications available for treatment of PCOS[7]

	Normal Doses	Common Side Effects
Metformin (Glucophage®)	500mg three times daily	Headache, gastrointestinal effects (nausea, diarrhea, flatulence) at initiation of therapy, weight loss, taste disturbances
Pioglitazone (Actos®)	15-45 mg once daily	Swelling, headache, respiratory infection, abdominal discomfort, muscle soreness
Rosiglitazone (Avandia®)	4-8 mg once daily	Headache, mild weight gain

Clinical Trials

One study performed by Dr. Antonio la Marca and his colleagues evaluated the effects of metformin (Glucophage®), a common insulin-sensitizing medication, in 12 overweight women, who had been diagnosed with PCOS.[8] After 1 month of receiving metformin 500mg three times a day, there was a significant decrease in the free testosterone levels of all patients and a significant increase in SHBG levels. Two of the women in this study ovulated without the use of fertility medications. These results allowed Dr. la Marca to conclude that the use of metformin caused a reduction in androgens for overweight patients with PCOS.

Another study by Dr. John Nestler and colleagues from the Medical College of Virginia specifically examined if PCOS patients would ovulate while receiving the same medication, metformin.[9] Dr. Nestler performed this study on 61 overweight PCOS patients. Thirty-five of the patients were selected to receive metformin 500mg three times a day for at least 35 days, while the remaining 26 received a placebo. At the end of the study, 89 percent of the women treated with metformin had ovulated successfully with or without the use of clomiphene, a common medication used to encourage ovulation. However, only 12 percent of the women who received the placebo had ovulated, even though they had received clomiphene. Other tests pointed out that the patients, who received metformin, had lower levels of insulin over the duration of the study. Dr. Nestler was able to conclude that PCOS patients were more likely to ovulate if their blood levels of insulin were decreased through the use of metformin.

A third study conducted by Dr. Andrea Dunaif evaluated the effects a different insulin-sensitizing agent, troglitazone (Rezulin®) on women with PCOS.[10] Twenty-one women were selected to receive either 200mg or 400mg of troglitazone. Women who received the higher dose had an overall decrease in the levels of active androgens. These results led to the conclusion that this agent may correct many symptoms associated with PCOS and provide a new option for treatment. However, the FDA has recently removed this troglitazone from the market due to its harmful effects on the liver. Fortunately, similar medications, pioglitazone (Actos®) and rosiglitazone (Avandia®), are available and are currently considered to be safe. They may produce similar positive effects in women with PCOS, however they have yet to be evaluated for the treatment of this condition.

Summary

Other agents are currently undergoing trials to evaluate their utility in the treatment of PCOS. Currently, insulin-sensitizing agents provide new hope for patients diagnosed with this disease. The discovery of the positive effects of these medications has pushed PCOS research in a new direction that provides a promising future.

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