



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

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PATIENT'S FACT SHEET

Insulin Sensitizing Agents and PCOS

Polycystic ovarian syndrome (PCOS) is a very common reproductive disorder. Women with PCOS frequently have irregular menstrual cycles, excessive body hair, are overweight, and suffer from infertility. Many women with PCOS have a decreased sensitivity to insulin for which their bodies compensate by overproducing insulin. The resulting high levels of insulin may contribute to excessive production of androgens (male hormones, such as testosterone) and contribute to ovulation disorders. In addition to reproductive problems, women with PCOS have a higher chance of developing medical problems such as Type 2 (non-insulin dependent) diabetes, high blood pressure, and heart disease. By the age of 40, up to 40% of PCOS patients develop impaired glucose tolerance or clinical diabetes.

Given the strong evidence that excess insulin plays a role in the development of PCOS, it is reasonable to assume that reducing circulating levels of insulin may help restore normal reproductive function. This may be accomplished by weight loss, improved nutrition, and exercise. These behavioral changes should be the first lines of therapy for an overweight woman with PCOS.

Recently, new drugs approved by the FDA for the treatment of Type 2 diabetes have shown promise for PCOS. These drugs, known as **insulin sensitizing agents**, have been shown to improve the body's response to insulin, thereby reducing the need for excess insulin and restoring the levels to normal. The best studied insulin sensitizing agent available in the United States for women with PCOS is **metformin** (Glucophage®), a biguanide. Metformin reduces circulating insulin and androgen levels and restores normal ovulation in some women with PCOS. Even if metformin alone does not restore ovulation, it may improve a woman's response to fertility drugs. Gastrointestinal irritation, especially diarrhea, is a common side effect. These symptoms usually improve after a few weeks. Lactic acidosis is a rare but serious adverse effect of metformin. Metformin is not recommended for patients with kidney, lung, liver, or heart disease.

Rosiglitazone (Avandia™) and **pioglitazone** (Actos®), which belong to the **thiazolidinedione** group of antidiabetic agents, are also available in the United States for women with PCOS. Thiazolidinediones have been shown to reduce hyperandrogenism and restore ovulation in some PCOS patients. Liver toxicity is the main concern with these agents. Liver tests should be performed every two months for the first year and periodically thereafter. These medications should not be started in women with any evidence of liver disease.

So far, the new insulin sensitizing agents have not been linked to birth defects in animals or humans, but they are not recommended for use during pregnancy. Metformin should also be temporarily stopped prior to surgery or X-ray procedures that use intravenous contrast.

Unlike ovulation induction drugs, insulin sensitizing agents have little or no risk of multiple pregnancies. More clinical studies are needed to determine the outcomes, risks, and complications when these medications are used to treat PCOS. Although results from clinical studies have been encouraging, the use of these medications in women with PCOS is still considered investigational. In general, Metformin is used as the first insulin sensitizing agent; thiazolidinediones may be considered if metformin is ineffective or not tolerated by the patient.

Present data suggest the use of insulin sensitizing agents for ovulation induction in PCOS patients who want to conceive. Because these medicines correct the underlying metabolic abnormalities associated with PCOS, it is plausible that their long-term use may delay the emergence or reduce the likelihood of developing Type 2 diabetes and cardiovascular disease. Since data are lacking, however, long-term use of insulin sensitizing agents for this purpose cannot be recommended at present.

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