**Metformin, rosiglitazone, or both for obese women with polycystic ovary syndrome?**

In this issue, Yujing et al. (1) compared the effects of the two most commonly used insulin sensitizers for obese, insulin resistant women with polycystic ovary syndrome (PCOS; by Rotterdam criteria). Two hundred four participants were randomized into three comparable groups. Group 1 received 1,500 mg metformin, group 2 received 4 mg of rosiglitazone, and group 3 received 1000 mg metformin plus 4 mg rosiglitazone for six months. In addition to drugs, dietary adjustment and moderate-strength physical exercises for 40 minutes three times a week were recommended to all groups. Homeostatic model assessed insulin resistance. Of interest were effects on average menstrual intervals, anthropometric measurements, androgens, and metabolic indices of insulin, carbohydrates, and lipids. Most participants showed an improvement in their menstrual pattern, as well as their metabolic indices. Serum free testosterone (T), acne scores, and anthropometric measures (weight, waist circumference, waist to hip ratio and body mass index) also improved. Metformin was associated with greater weight loss. Rosiglitazone alone or in combination was better in reducing total cholesterol and triglyceride levels. However, better predictors of cardiovascular disease risk (total cholesterol/high-density lipoproteins and low-density lipoproteins/high-density lipoproteins ratios) were improved equally in all three groups.

Dietary changes and exercise activities for all participants were monitored, yet compliance or quantification of these lifestyle modifications by each group is not reported. Lifestyle changes may have contributed significantly to the findings in all three treatment groups. In the Diabetes Prevention Program, diet and exercise were more effective for diabetes prevention than metformin. There is considerable regional and ethnic diversity in lifestyle modifications; the effects of insulin sensitizer when combined with lifestyle modifications can be varied. Block randomization was used. Baseline demographic and clinical characteristics were comparable in all three groups. The study was open label; the influence of knowledge of treatment arm on outcome is possible. The outcomes of interest were objective minimizing the role of perception. Among 204 matched participants, 19 withdrew, leaving 185. Intention to treat analysis was applied. Overall, this is a well-conducted randomized controlled trial with appropriate statistical analysis.

In a prior study of non-obese women with PCOS yet normal indices of insulin sensitivity, Bailargeon et al. (October 2004) studied a combination of the same insulin-sensitizing drugs versus either alone. One hundred women were randomized to twice-daily use of one of the following: 850 mg metformin; 4 mg rosiglitazone; combination of both drugs; and placebo, all with dietary and exercise recommendation for 6 months. Frequencies of ovulation and serum free-T were noted after 6 months intervention. Treatment with either insulin-sensitizing drug improved the frequencies of ovulation compared to placebo; better with metformin than rosiglitazone. The combination was no better than either in isolation. Both drugs were equally good in ameliorating hyperandrogenemia. Metformin improved insulin sensitivity compared to rosiglitazone. Two different populations of women with PCOS (Yujing et al. 2019 and Bailargeon et al. 2004) were studied with these agents in the randomized controlled trials mentioned previously.

In 1995 the Food and Drug Administration approved metformin for non-insulin-dependent diabetes mellitus (NIDDM). It appears to act by suppressing hepatic glucose production and enhancing insulin sensitivity. Metformin is the most commonly used insulin sensitizer for PCOS. It improves metabolic derangements, it helps in weight loss and it ultimately improves ovulation (2). Overall, metformin has a good safety profile, although megaloblastic anemia (from decreased folic acid and/or vitamin B12 absorption) and lactic acidosis have been reported occasionally. Vitamin B12 deficiency can lead to neuropathy. Lactic acidosis is usually in the presence of predisposing conditions e.g. cardiorespiratory insufficiency, renal or liver failure, history of ketoacidosis, and severe dehydration. Gastrointestinal side effects are the most frequently reported adverse effects with metformin (up to 20%-30%), fortunately tending to be transient and can be reduced by gradually increasing the dose (2). The other insulin sensitizer, rosiglitazone, was approved by the Food and Drug Administration for NIDDM in 2002. It is a peroxisome proliferator-activated receptor-γ agonist. It improves insulin sensitivity by influencing the transcription of a variety of genes implicated in carbohydrate and lipid homeostasis (3).

Troglitazone (another drug from same group) was withdrawn from the market due to hepatotoxicity. No such adverse effect have been reported for rosiglitazone. Fixed-dose combination of rosiglitazone/metformin is approved and is available in the U.S., indicated when NIDDM is not well controlled with a single drug. Yujing et al. (1) reported no side effects related to rosiglitazone in their study. Metformin was well tolerated or gradually adapted within 1 week to 5 weeks although one patient withdrew due to intolerance. Unfortunately, the compliance to metformin in the general population is lower than in the current study. Drug interactions and economic considerations are important, e.g., cimetidine reduces renal tubular secretion of metformin, and hence metformin dose should be reduced if these drugs are used together. Metformin is available at a discounted price of $4 for 30 tablets of 1,000 mg. In comparison, rosiglitazone is still expensive. Average cost is US $200 for 30 tablets of 4 mg. Regular monitoring of liver enzymes is recommended for both agents even though they do not share the hepatotoxic profile of troglitazone (4). PCOS is associated with obesity, insulin resistance and NIDDM, which are associated with liver abnormalities, especially non-alcoholic steatohepatitis. Assessing baseline liver function is important prior to starting such treatment.

Another important consideration is the effect of these medications when used pre-conception or during pregnancy. Rosiglitazone was classified as a category C drug. Conception should be assured. Overall, metformin is considered safe
as a first-line treatment for gestational diabetes mellitus. There is no convincing evidence associating metformin exposure in early pregnancy with congenital malformations or miscarriage. Prenatal exposure is associated with increased neonatal weight. Larger long-term follow-up studies are needed to confirm possible metabolic programming effects [5]. Yujing et al. [1] have made an important contribution for treating obese insulin resistant women with PCOS. The study is of short duration. We have limited understanding of persistent benefits with continued use and if short-term benefits translate into decreased cardiovascular disease events. The specific patient population needs to be taken into account when extrapolating the findings. Long-term risks and benefits of different treatments need further exploration.

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https://doi.org/10.1016/j.fertnstert.2019.10.006

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