FPIN's Help Desk Answers

Alternatives to Metformin for Patients with PCOS

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Help Desk Answers provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/?o=1025).

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Clinical Question

What is the best insulin-sensitizing medication for patients with polycystic ovary syndrome (PCOS) who cannot tolerate metformin?

Evidence-Based Answer

Compared with placebo, thiazolidinediones (TZDs) decrease systolic blood pressure and fasting blood glucose and insulin levels while improving menstrual irregularities in women with PCOS. (Strength of Recommendation: A, based on a meta-analysis of randomized controlled trials [RCTs].) Metformin and TZDs have similar effects on pregnancy rates, ovulation, and menstrual frequency, but TZDs can cause weight gain and lower free testosterone and dehydroepiandrosterone (DHEA) levels to a greater degree, whereas metformin reduces body mass index (BMI) and serum triglyceride levels to a greater degree.

A 2012 systematic review of 44 RCTs (N = 3,992) evaluated metabolic and reproductive outcomes for insulin-sensitizing drugs, including metformin, rosiglitazone (Avandia), pioglitazone (Actos), and D-chiro-inositol (a dietary supplement involved in insulin signal transduction) in women with oligomenorrhea, subfertility, and PCOS (defined as meeting at least two of the 2003 Rotterdam consensus criteria).[1] Only six of the 44 studies involved agents other than metformin; two studies used rosiglitazone (N = 100; 4 mg once or twice daily), two used pioglitazone (N = 70; 30 mg daily), and two used D-chiro-inositol (N = 327; 100 mg to 1,200 mg daily). Menstrual cycle regularity improved with rosiglitazone (odds ratio [OR] = 5.6; 95% confidence interval [CI], 2.2 to 14.2) and pioglitazone (OR = 8.9; 95% CI, 2.4 to 33.6) compared with placebo. Patients receiving rosiglitazone had a slightly lower systolic blood pressure (mean difference = –2.0 mm Hg; 95% CI, –4.0 to –0.05) compared with placebo. D-chiro-inositol was evaluated in two trials of obese women (mean BMI = 31 to 33 kg per m^2) with PCOS diagnosed by oligomenorrhea, elevated testosterone level, or hirsutism. In these studies, D-chiro-inositol had no effect on ovulation rates, BMI, blood pressure, or hormonal or metabolic outcomes compared with placebo.

A 2011 meta-analysis of 10 controlled studies (six RCTs and four studies with unclear randomization procedures, N = 459) compared clinical, hormonal, and metabolic outcomes, and tolerability of metformin vs. TZDs at three months and six months in women with varying BMIs (22 to 36 kg per m^2) who were diagnosed with PCOS.[2] Metformin (500 to 2,500 mg per day) was superior to TZDs in reducing BMI at three months (five studies, N = 209; weighted mean difference [WMD] = –2.47 kg per m^2; 95% CI, –3.3 to –1.6) and at six months (four studies, N = 199; WMD = 0.70 kg per m^2; 95% CI, –0.76 to –0.65), but had a higher risk of adverse gastrointestinal effects at three months (five studies, N = 215; OR = 8.9; 95% CI, 3.5 to 22.3) and at six months (three studies, N = 149; OR = 12.2; 95% CI, 3.5 to 42.3), resulting in a 2% withdrawal rate in three of the studies. The most common adverse effect for TZDs was headache. At three months, TZDs reduced free testosterone levels (three studies, N = 139; standardized mean difference [SMD] = –0.36; 95% CI, –6.9 to –0.03) and DHEA levels (four studies, N = 173; SMD = –0.49; 95% CI, –0.79 to –0.18) more than metformin. (An SMD of 0.2 is considered small, 0.6 moderate, and 1.2 large.) At six months, metformin reduced triglyceride levels more than TZDs (two studies, N = 61; SMD = 1.1; 95% CI, –1.7 to –0.57). There was no statistically significant difference between metformin

and TZDs for ovulation rates, pregnancy rates, menstrual frequency, or general lipid profiles at either time interval.

A 2012 meta-analysis of eight RCTs (four using pioglitazone [N = 114; 30 or 40 mg per day] and four using rosiglitazone [N = 172; 4 mg once or twice daily]) analyzed the effectiveness of TZDs in the treatment of PCOS compared with placebo.[3] The study populations were not limited by age or BMI, and study outcomes included insulin and fasting blood glucose levels, degrees of hirsutism (using the Ferriman-Gallwey scale), serum androgen levels, and BMI. TZDs improved insulin levels (seven studies, N = 234; SMD = –0.81; 95% CI, –1.5 to –0.12) and fasting blood glucose levels (six studies, N = 219; SMD = –0.55; 95% CI, –1.1 to –0.05) compared with placebo, but had no effect on androgen levels or hirsutism. TZDs led to an increase in BMI (seven studies, N = 231; SMD = 0.39; 95% CI, 0.13 to 0.66).

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