The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome

Richard S. Legro, MD; Richard J. Zaino, MD; Laurence M. Demers, PhD; Allen R. Kunselman, MA; Carol L. Gnatuk, MD; Nancy I. Williams, ScD; William C. Dodson, MD

OBJECTIVE: To examine the effects of metformin and rosiglitazone, alone and in combination, on endometrial histology and ovarian steroid production.

STUDY DESIGN: Randomized open-label study of metformin and rosiglitazone in 16 women with polycystic ovary syndrome (PCOS) performed at a single academic health center. The study consisted of a 6-week baseline observation period, a 3-month treatment period of single-agent therapy (rosiglitazone or metformin), and then a 3-month period of combined therapy.

RESULTS: Abnormal endometrial histology was found in 3 subjects at baseline, including 1 case of adenocarcinoma of the endometrium in an asymptomatic subject, who was excluded from further study. The 2 other abnormal cases (simple hyperplasia) resolved with treatment. Three months of single-agent therapy showed a benefit of rosiglitazone (n = 9) over metformin (n = 6) in terms of reducing circulating unbound testosterone levels (−11.8; 95% CI: −21.7 to −2.0 ng/dL) and 2-hour glucose (−42.0; 95% CI: −76.2 to −7.8 mg/dL), 2-hour insulin (−150.4; 95% CI: −272.7 to −28.1 μU/mL) as well as a significant decrease in integrated levels of glucose and insulin by area under the curve analysis, all obtained from oral glucose tolerance testing. Daily urinary progestin-to-estrogen ratios improved on rosiglitazone compared to metformin therapy (0.08; 95% CI: 0.02 to 0.14). Ovulatory rates tended to improve on both single-agent and combined treatments (30/90 cycles, 33%), compared to baseline ovulatory rate (2/15, 13%). Despite 6 months of therapy alone or in combination, 5 women displayed no evidence of biochemical ovulation by urinary or serum progestin measurements.

CONCLUSION: This study provides preliminary evidence that insulin-sensitizing drugs may have beneficial effects on the endometrium, although the exact mechanism beyond improving ovulatory function is still unknown. In addition, we suggest that rosiglitazone may be more beneficial than metformin therapy on raised insulin and androgen levels in an obese PCOS population. Combined therapy did not demonstrate significant benefit above and beyond single-agent therapy.

Key words: endometrial histology, endometrial hyperplasia, hyperandrogenism, insulin resistance, urine

Cite this article as: Legro RS, Zaino RJ, Demers LM, et al. The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol 2007;196:402.e1-402.e11.

Polycystic ovary syndrome (PCOS) is characterized by several reproductive abnormalities including elevated circulating androgen levels, chronic anovulation, and polycystic ovaries.[1] The fundamental pathophysiologic defect is still unknown, but PCOS women are frequently insulin resistant.[2] The lack of a clear etiologic mechanism to explain the syndrome has led to a multitude of symptom-oriented treatments with few therapies improving all aspects of the endocrine disorders that are characteristic of PCOS.

Drugs that improve insulin action have consistently been found to improve the reproductive abnormalities observed in PCOS women, including improvements in ovulatory frequency and reduced hirsutism.[3,4] The mechanisms are still not completely understood, although common endpoints that tend to improve in responders include both circulating insulin and androgen levels,[4,5] suggesting that both hyperinsulinemia and hyperandrogenemia contribute to the clinical manifestations of the syndrome. These drugs have now become cornerstones of treatment for PCOS, although few studies have compared insulin sensitizers head to head or in combination in women with PCOS.[6]

Although these medications have been shown to be frequently effective, they do

From the Departments of Obstetrics and Gynecology (Drs Legro, Gnatuk, and Dodson), Pathology (Drs Zaino and Demers), and Health Evaluation Sciences (Mr Kunselman), The Pennsylvania State University College of Medicine, Hershey, PA, and the Department of Kinesiology, Noll Laboratory, The Pennsylvania State University College of Health and Human Development, University Park, PA (Dr Williams).

Presented at the 25th Annual Meeting of the American Gynecological and Obstetrical Society, Williamsburg, VA, Sept. 14-16, 2006.

Funding was provided by Public Health Service grant K24 HD001476 (R.S.L.), General Clinical Research Center grant M01 RR010732, and construction grant C06 RR016499 (The Pennsylvania State University), and the CROWN Foundation, Lancaster, PA.

Received Nov. 10, 2006; accepted Dec. 18, 2006.

Reprints: Richard S. Legro, MD; RSL1@psu.edu

0002-9378/$32.00

doi: 10.1016/j.ajog.2006.12.025

not completely restore a normal reproductive phenotype.[7] For example, many women with PCOS do not ovulate in response to insulin sensitization, even at the highest doses, and those who do respond experience an increase in ovulatory frequency but still are oligoovulatory.[4,7] As with other complex medical disorders such as diabetes and hypertension, multiagent therapy is required to fully treat the symptoms and biochemical abnormalities characteristic of PCOS.[8,9]

A combination of metformin and a thiazolidinedione (troglitazone) was found to be superior in the treatment of type 2 diabetes compared to single-agent therapy alone, with additive benefits in the lowering of glucose and insulin levels in this disorder.[10] Troglitazone was subsequently removed from the world market due to its hepatotoxicity, but similar findings have been noted with the newer thiazolidinediones, including rosiglitazone. Inferentially, the same combined benefit may exist for women with PCOS, given that the degree of insulin resistance among women with PCOS is comparable to that of women with type 2 diabetes.[11]

Another area that has only been superficially explored in clinical trials is the endometrial effects of insulin-sensitizing agents. Women with PCOS have been reported to suffer from increased pregnancy loss[12] and also are at increased risk for endometrial cancer.[13] These areas of concern are important not only because of the potential effects of these drugs on the endometrium, including effects on implantation and early pregnancy, but because of the suspected long-term increased risk of endometrial hyperplasia and cancer among women with PCOS.[14] Endometrial function must be studied concurrently with ovarian function, given the intimate link between the two.

We conducted this study to examine the combined effects of metformin and rosiglitazone compared to single-agent therapy on ovarian steroid production and excretion and on endometrial histology in women with PCOS. Specifically, we hypothesized that combined treatment would result in the highest ovulatory frequency, compared to single-agent therapy, and a greater restoration of cyclical ovarian activity. We also examined endometrial histology from sequential endometrial biopsies.

Materials and Methods

The study encompassed 30 weeks in women with PCOS, beginning with a prerandomization visit, a 6-week medication-free observation period, followed by randomization to metformin or rosiglitazone in an open-label trial. Once randomized, the women were followed for 12 weeks of single-agent therapy, which was followed by a subsequent 12 weeks of combined treatment with both agents.

Subjects

The Investigational Review Board at the Pennsylvania State College of Medicine approved this study and all subjects gave written informed consent. We recruited women with PCOS aged 18-40 years who were euthyroid nonsmokers in good health and who, for at least 1 month prior to each study, were not taking any medications known to affect sex hormone metabolism or glucose metabolism; contraceptive steroids were stopped for at least 3 months. We defined PCOS as an elevation of circulating androgen levels, either total testosterone $>$ 58 ng/dL or free and weakly bound testosterone levels $>$ 16 ng/dL, associated with chronic oligomenorrhea ($\leq$ 6 menses per year) or amenorrhea.[15]

Women with nonclassical 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate testing. Other exclusion criteria were pregnancy, baseline elevations in liver function tests or abnormalities in renal function, type 2 diabetes, anemia, thrombocytopenia, and significant hypertension. Study participants were instructed to use barrier contraception during the study to avoid pregnancy.

Study procedures

Height, weight, hip-to-waist ratio, blood pressure, and Ferriman-Gallwey assessment of hirsutism were obtained at all visits.[16] Women presented fasting at the prerandomization visit and underwent an exam with fasting blood samples obtained for analysis of sex steroids, glucose, insulin, and safety labs (renal and liver profile, complete blood count, and urine pregnancy test). The women were instructed to record a menstrual diary throughout the study and were advised to adhere to a constant diet and not institute any change in their exercise regimen over the course of the study. They were instructed to collect an early-morning urine sample daily during the study. They were then observed for 6 weeks prior to randomization to establish their baseline ovulatory frequency and ovarian function.

After the 6-week observation period, the subjects were randomized to either 1000 mg twice a day of metformin or 4 mg twice a day of rosiglitazone, using a permuted-blocks scheme with blocks of size 10. Metformin was given in 2 divided doses and increased in stepwise increments from 500 mg a day until the target dose of 2000 mg a day was reached. On the day of the randomization visit, subjects had a transvaginal ultrasound, a 75-g oral glucose tolerance test (OGTT), and an endometrial biopsy. All OGTTs during the study were performed at 0800-1000 hours after a 3-day, 300-g carbohydrate diet and an overnight fast of 10-12 hours. Studies were performed in women with PCOS, all of whom were oligoovulatory, without regard to the last episode of vaginal bleeding.

An intravenous catheter was inserted and the vein was kept open with an infusion of 0.9% normal saline at 30 mL/hour. All subjects received a 75-g oral glucose load and blood samples were obtained at 0 and 120-minutes. Additional blood samples were obtained at 30, 60, 90, and 180 minutes. An insulin sensitivity index ($ISI_{0,120}$) was calculated based on the fasting (0 minute) and 120-minute OGTT glucose and insulin levels; this index is highly correlated with the rate of whole-body glucose disposal determined by the euglycemic-hyperinsulinemic clamp technique.[17]

Upon completion of the OGTT, a transvaginal ultrasound of the pelvis was performed. The following measures were obtained: endometrial thickness,