Effects of metformin in adolescents with polycystic ovary syndrome undertaking lifestyle therapy: a pilot randomized double-blind study

Our small study does not support the addition of metformin to the lifestyle of adolescents. Although there are favorable trends toward hyperandrogenism with metformin, these must be balanced against the increased rate of gastrointestinal side effects. However, other treatments were associated with an improved quality of life. (Fertil Steril® 2011;95:2595–8. ©2011 by American Society for Reproductive Medicine.)

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Adolescents with polycystic ovary syndrome (PCOS) are difficult to manage clinically because of the lack of well-designed studies showing treatment safety and efficacy. In addition, this is a vulnerable population, so studies must be balanced to withstand increased scrutiny. Adolescents may be less compliant with recommended therapies because of immaturity. However, this population represents an enormous opportunity to intervene early in the ontogeny of PCOS, especially when linked to obesity. Randomized studies of metformin in girls with premature pubarche show delays in pubertal development and a relative protection against developing PCOS post menarche (1, 2).

Treatments such as metformin have been studied extensively in adolescents with type 2 diabetes and found to have a safe risk–benefit ratio (3). There are fewer data in adolescents with PCOS. Lifestyle therapy in obese women with PCOS has become, at least according to expert opinion, a cornerstone (4, 5). In addition, the addition of metformin has been associated with increased weight loss when combined with lifestyle interventions (6). We sought to establish the risk–benefit ratio of lifestyle therapy combined with and without metformin therapy over 6 months in obese adolescent females with PCOS and designed a trial very similar to our recent trial in adults (7). We hypothesized that the combination of lifestyle and metformin would be superior to lifestyle alone in improving serum testosterone levels, an important biomarker of PCOS.

The IRBs of the Meharry Medical College and Penn State College of Medicine approved the study. Subjects aged 13–18 years and with a BMI >27 kg/m^2 were enrolled between 2004 and 2008 and all gave written informed consent. We used the 1990 NIH/NICHD PCOS diagnostic criteria to identify subjects (8): chronic anovulation, defined as spontaneous intermenstrual periods of ≥ 45 days or a total of ≤ 8 menses per year, and hyperandrogenism defined as an elevated total testosterone (>50 ng/dL) or a free androgen index (FAI = ratio of testosterone/sex hormone–binding globulin (SHBG) (100)) >1.5 (9). Other causes were excluded by appropriate tests. Subjects were in good general health and off confounding medications.

The a priori primary outcome was the change in serum testosterone level. The study was powered to detect a 25% absolute difference in serum testosterone levels using a two-sided test having

a type I error of 5% with at least 80% power and assumed projected subject dropout rate of 15%. On the basis of a log-normal distribution and a 30% coefficient of variation, 50 subjects per treatment arm were required. Subjects were randomized for this double-blind study in a 1:1 allocation ratio using a computer-generated random number table with permuted blocks and stratified by center and prior metformin exposure status after a baseline visit.

All subjects received the lifestyle intervention (and described in more detail in the Supplemental Materials and Methods, available online) (7). A combined intervention of diet and exercise was employed with the goal of achieving an average weight loss of at least 7% from initial body weight over 6 months, with a prescription of 150 minutes/week of exercise combined with a low-calorie diet (10). The exercise program consisted of supervised and nonsupervised components (without polar heart rate monitoring in adolescents) to maximize flexibility and acceptance of the intervention (7). Subjects were given the opportunity to attend a fitness facility operated by the research team at least 2 sessions per week.

Metformin hydrochloride was obtained as a powder (Spectrum Chemical Manufacturing), formulated with a 500-mg dose of drug per capsule with identical placebo capsules by the Investigational Pharmacies in a double-blind fashion (7, 11). Medication was initiated in a step-up fashion every 5 days, from one tablet a day to four. This dose was maintained as tolerated throughout the remainder of the study.

The patients were seen monthly and underwent submaximal exercise testing on a stationary bicycle. Hirsutism was assessed using the modified Ferriman-Galwey score (12). Facial lesions counts of open and closed comedones (noninflammatory lesions) were obtained from the forehead, left, and right cheeks, nose, and chin (13). Serum was obtained for hormone measurements. Testosterone was measured by RIA (14) and SHBG was determined by chemiluminescence using a Siemens Immulite platform. In addition, at baseline and study completion after 6 months, subjects completed a quality-of-life survey, a 75-g oral glucose tolerance test, a transabdominal ovarian ultrasound, and a dual-energy x-ray absorptiometry (DXA) scan using a total-body scan and dual hip scans with the fan-beam mode of a Hologic QDR-4500W (Hologic Inc.). Subregion analysis of visceral and central abdominal fat was modeled (15). The validated PCOS Questionnaire, measuring health-related quality of life in women with PCOS, includes five domains (16). Each domain score is graded on a scale of 1 (poorest function) to 7 (optimal).

Linear mixed-effects models were fit to continuous outcomes to compare metformin to placebo with respect to the change from baseline measurement (17). The number of bleeding episodes and the adverse event rates were compared between the two treatment arms using Poisson regression models. All analyses followed the intention-to-treat principle and we reported mean ± SD. No adjustments for multiple hypothesis testing were performed because all outcomes, other than the primary, were considered to be exploratory. All hypothesis tests were two-sided and all analyses performed using SAS software (version 9.1, SAS Institute Inc.).

We screened 28 patients and randomized 22 (20 Caucasian and 2 African American) (Supplemental Fig. 1). The two treatment groups were similar at baseline for all parameters. Mean age for MET was 16.1 ± 1.5 years versus 15.4 ± 1.2 years for PBO, mean BMI was 37.1 ± 5.8 for MET versus 35.9 ± 6.6 for PBO (Supplemental Table 1). On ultrasonographic exam, all subjects in the MET group had polycystic ovaries by consensus criteria (18) and 9 subjects in the PBO group (2 girls in PBO did not have ultrasound visualization of their ovaries). Thus, all girls who were fully phenotyped met all of the Rotterdam criteria for PCOS. Only four subjects dropped out of the study (1 for MET and 3 for PBO). The addition of metformin to lifestyle resulted in a significant decrease in serum testosterone and FAI at 3 months compared with baseline and lifestyle alone, and at 6 months compared with baseline (Fig. 1A and B). Further, there was a significant reduction in acne, a marker of hyperandrogenism, at every visit compared with baseline in the MET group (Fig. 1C), and no significant change in weight (Fig. 1D). Moreover, there were no changes in waist measurement, blood pressure, hirsutism scores, lipid parameters, VO_2max, or in ovarian volume or maximum follicle size during the study (Supplemental Table 2). There was no difference in the number of menstrual bleeding episodes in the MET group compared with the PBO group (rate ratio [RR] = 1.7, 95% CI = 0.7, 3.9, P=.22). There were significantly more adverse events in the MET group compared with the PBO group for stomach or abdominal pain (RR = 3.6, 95% CI = 1.0, 12.8, P=.05) and diarrhea (RR = 4.5, 95% CI = 1.5, 13.2, P=.01). There were no serious adverse events in either group.

Our trial in adolescents showed no benefit of MET over PBO on our primary outcome of serum testosterone levels at 6 months (though it did at 3 months); however, we did note improvements in acne, a peripheral marker of hyperandrogenism at various time points in both groups. In comparison with our larger study in adults (7), this study had a much higher retention rate, although the sample size was small (82% retention in adolescents and 33% retention in adults). This higher retention rate could be due to support of the parents, our relative lack of minority participation (compared with our adult study), or the more streamlined protocol in adolescents with less monitoring of diet and exercise and lack of daily urine collections. Also, the favorable improvements in overall quality of life (compared with baseline) in both treatment groups, may have supported further participation in the study (19). Our data suggest that the benefits of our interventions waned from 3 to 6 months, and the diminished compliance with our lifestyle recommendations was probably a factor as we noted no improvement in VO_2max in either group.

We failed to recruit our projected sample size, so our findings are somewhat surprising given our limited sample size. The primary barrier to recruitment was the number of subjects interested in the study, as patients who consented to screening were likely to participate in the study. There are few studies of combined lifestyle and insulin-sensitizing therapy in adolescents with PCOS. Our findings are consistent with the largest and most similar study performed in adolescents (20). In a preliminary single therapy trial reported in this paper, lifestyle modification over 24 weeks showed a significant improvement in free androgen index (through SHBG increase) and no change in hirsutism as in our study (nor would this be expected in 6 months), but did not track acne changes. Similarly, the present study noted no changes in weight or waist circumference at the completion of 24 weeks. In a second trial in this same paper (20), Hoeger et al. compared metformin with lifestyle plus oral contraceptives to placebo with lifestyle plus oral contraceptives and found in the lifestyle plus metformin arm a significant decrease in both weight and waist, whereas our subjects gained weight albeit minimal.