Effects of short-term and long-term metformin treatment on menstrual cyclicity in women with polycystic ovary syndrome

The purpose of this retrospective study was to compare the frequency of menstrual cyclicity between two groups of patients with polycystic ovary syndrome: women who were followed while on metformin for 3–6 months and those who were followed for >6 months. The results showed that metformin is highly effective in normalizing menstrual cyclicity in women with polycystic ovary syndrome (the overall response rate was 69%, with 88% of responders achieving normal cyclicity), especially with a treatment duration of 6 months or longer (the response rate was 40% higher for women who were treated with metformin for >6 months vs. 3–6 months, 77% vs. 55%). (Fertil Steril® 2006;86:230–2. ©2006 by American Society for Reproductive Medicine.)

Insulin resistance with compensatory hyperinsulinemia plays a major pathogenic role in both lean and obese women with polycystic ovary syndrome (PCOS) (1). Of the insulin-sensitizing agents, metformin has been the most extensively studied for the treatment of PCOS. To date, no large study has evaluated the influence of the duration of metformin treatment on menstrual cyclicity and response rate in PCOS.

Our specific aims were to [1] compare the frequency of menstrual cyclicity between women with PCOS on metformin for 3–6 months versus >6 months and [2] compare baseline clinical, demographic, and endocrine characteristics of responders and nonresponders to metformin treatment. We chose the 3- to 6-month interval because it has been documented that most discontinuations of metformin, usually for side effects, occur before 3 months of use (2). Therefore, the 3- to 6-month group would represent women who tolerated the drug and in that sense would be comparable to the >6 month group.

We conducted a retrospective medical chart review of all women with PCOS seen by two of the authors (J.E.N., M.J.I.) in the private Endocrine Clinic of the Virginia Commonwealth University Medical Center for routine clinical care from December 2000 to December 2003. PCOS was diagnosed using the 1990 National Institutes of Health criteria (3). As per the practice of the clinic, >95% of women with PCOS were treated with metformin, regardless of body mass index (BMI), based on the strength of evidence supporting metformin use in PCOS. Women were treated with metformin 2,000 mg/d or the maximally tolerated dose in an attempt to achieve the greatest effect of metformin. Inclusion criteria were [1] no use of medications known to affect sex steroid metabolism and menstrual cyclicity, such as oral contraceptives or insulin-sensitizing drugs, for ≥3 months before the study period; [2] documented use of metformin for ≥3 months during the study period; and [3] recorded history of menses throughout the study period.

Oligomenorrhea was defined as 3–8 menstrual cycles per year, amenorrhea as <3 menstrual cycles per year (4), and normal cyclicity as 9–12 menstrual cycles per year, or 0.75–1 per month. A positive response to metformin treatment was classified as either [1] normalization of frequency from either amenorrhea or oligomenorrhea or [2] transition from amenorrhea to oligomenorrhea. Patients were required to maintain menstrual cycle logs. When improvement in menstrual cyclicity was noted, ovulation was always confirmed by an appropriately increased luteal phase serum P level (>3 ng/dL) on menstrual cycle day 21 during two or more subsequent cycles.

Results are reported as means with 95% confidence intervals (CIs) or percentages. Analysis of covariance was used to adjust for baseline differences of menstrual cyclicity for comparisons of menstrual cycle frequency at follow-up. For comparison of continuous variables, the Student's *t*-test was used. Demographic and historic dichotomous variables were compared by χ^2 analysis using the Pearson test. $P<.05$ was considered statistically significant, and statistical analysis was performed using JMP version 4.0 (SAS Institute Inc., Cary, NC). Institutional Review Board approval was obtained.

Of the total 116 women who met the inclusion criteria, 11 (9.5%) were excluded because of inadequate information on menstrual cycle frequency, leaving a total of 105 patients for inclusion in the study. Excluded individuals

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were older than included individuals (33.5 vs. 27.9 years; $P = .02$) but did not differ with regard to demographic, clinical, endocrine, or metabolic characteristics.

The women studied were treated with metformin for 10.5 ± 9.0 months (mean ± SD), with a range from 3 to 48 months. Those who discontinued metformin before 6 months did so primarily because of intolerance to gastrointestinal side effects. The overall rate of response to metformin therapy (improvement in menstrual cyclicity) was 69% (95% CI, 0.59–0.77).

Of the 72 responders, 41 (57%) went from amenorrhea to normal cyclicity, 22 (31%) from oligomenorrhea to normal cyclicity, and 9 (12%) from amenorrhea to oligomenorrhea. The mean frequency of menstrual cyclicity improved significantly from 0.27 per month (95% CI, 0.23–0.31) to 0.70 per month (95% CI, 0.63–0.77; $P<.0001$) with metformin treatment. There was a mean duration of two cycles for improvement in menstrual cyclicity to be observed, with no significant differences based on duration of therapy. There was no correlation between weight change and response to metformin ($P = .12$).

The response rate of women followed for >6 months (77% [50/65]) was 40% higher ($P = .02$) than that of women followed for only 3–6 months (55% [22/40]). In addition, the frequency of menstrual cyclicity at the last follow-up visit was significantly higher ($P<.001$) in women followed for >6 months (mean of 0.76 cycles per month; 95% CI, 0.67–0.84) compared with those followed for 3–6 months (mean of 0.60 cycles per month; 95% CI, 0.50–0.71).

Responders were similar to nonresponders in age (27.5 vs. 29.4 years, respectively; $P = .39$), BMI (35.5 vs. 36.2 kg/m^2, respectively; $P = .74$), age at menarche (12.3 vs. 12.8 years, respectively; $P = .50$), and family history (Table 1). There were no differences in response rates to metformin treatment between African-American and Caucasian patients ($P = .40$). Levels of serum total T (88.4 vs. 64.4 ng/dL; $P<.001$) and free T (1.7 vs. 1.3; $P = .04$, respectively) were higher in nonresponders compared with responders. Similarly, levels of serum total cholesterol (210.5 vs. 189.4 mg/dL; $P = .03$) and triglycerides (208.5 vs. 130.9 mg/dL; $P<.001$) were higher in nonresponders than in responders.

Our findings indicate that for the entire study group, a high percentage of women (69%) responded to treatment with metformin, with 88% of responders achieving normal cyclicity regardless of whether they presented with oligomenorrhea or amenorrhea. Women treated with metformin

TABLE 1

Baseline clinical and endocrine characteristics of the two groups of patients with PCOS (n = 105).

Variables	Responders (n = 72)	Nonresponders (n = 33)	*P*
Age (y)	27.5 (25.7–29.2)	29.4 (26.2–31.4)	.39
Age at menarche (y)	12.3 (12.2–13.1)	12.6 (11.7–12.9)	.46
Menstruation frequency (per month)	0.29 (0.25–0.34)	0.21 (0.15–0.29)	.06
Body mass index (kg/m^2)	35.5 (33.4–37.6)	36.2 (33.1–39.2)	.74
Systolic BP (mmHg)	120.4 (116.6–124.2)	121.0 (115.4–126.7)	.86
Diastolic BP (mmHg)	77.1 (74.6–79.6)	78.3 (74.6–82.0)	.58
Total T (ng/dL)	64.4 (57.1–71.8)	88.4 (77.5–99.3)	<.001
Free T (ng/dL)	1.3 (1.1–1.5)	1.7 (1.4–2.1)	.04
Sex hormone–binding globulin (nmol/L)	33.5 (28.5–38.5)	25.9 (16.9–34.8)	.14
17 α-hydroxyprogesterone (ng/dL)	98.4 (81.9–114.9)	101.3 (72.4–130.2)	.86
DHEAS (μg/dL)	228.7 (177.6–280.4)	174.9 (91.8–258.0)	.28
Total cholesterol (mg/dL)	189.4 (178.5–200.2)	210.5 (194.5–226.5)	.03
LDL cholesterol (mg/dL)	114.6 (106.4–122.8)	127.6 (115.2–140.0)	.09
HDL cholesterol (mg/dL)	46.1 (42.8–49.5)	44.3 (39.3–49.2)	.53
Triglycerides (mg/dL)	130.9 (107.1–154.8)	208.5 (172.4–244.6)	<.001
Fasting plasma glucose (mg/dL)	84.6 (81.2–87.535)	88.0 (82.8–93.8)	.26

Note: Responders improved menstrual cyclicity on metformin treatment. BMI = body mass index; BP = blood pressure. Data are presented as means and 95% confidence intervals. Metformin treatment duration for the entire group was 10.5 ± 8.99 months (mean ± SD), ranging 3 to 48 months. To convert values for 17 α-hydroxyprogesterone to pmol/L, divide by 0.0331; to convert DHEAS to μmol/L, multiply by 0.027; to convert sex hormone–binding globulin to μg/dL, divide by 34.674; to convert total T to pmol/L, multiply by 34.764; to convert values for free T to pmol/L, multiply by 34.764; to convert total cholesterol HDL-C and LDL-C values to mmol/L, multiply by 0.0259; to convert triglycerides values to mmol/L, multiply by 0.0113; and to convert glucose values to mmol/L, multiply by 0.0555.

Essah. Metformin in treatment of PCOS patients. Fertil Steril 2006.

for only 3–6 months demonstrated a lower response rate (55 % vs. 77%, respectively) and less improvement in frequency of menstrual cycles (0.60 vs. 0.76 cycles per month, respectively) compared with women who were treated for >6 months.

In addition, women with PCOS who failed to respond to metformin suffered from worse baseline hyperandrogenism and hyperlipidemia compared with responders. While insulin sensitivity was not determined directly, the heightened hyperandrogenism and hypertriglyceridemia of the nonresponders may have reflected a more severe insulin-resistant state (5). Therefore, failure to respond to metformin suggests that metformin is unable to sufficiently enhance insulin sensitivity in severely affected patients.

Although several studies have reported on the effect of metformin therapy on menstrual cyclicity (6), only three published trials have specifically evaluated whether resumption of normal menses was equated with ovulation. In a study by Glueck et al. (7), metformin was given to 43 women with PCOS (16 for <3 months, 12 for 3–6 months, and 15 for >6 months). Results showed that 91% (n = 39) of the women resumed normal menses, with the percentage of women resuming normal menses not differing among groups. Of six women who resumed normal menses, five (83%) were found to be ovulatory based on a single luteal phase serum P.

Similarly, in an open-label trial, Moghetti et al. (8) reported that menstrual cyclicity improved in 17 (54.8%) of 32 women treated with metformin for a mean duration of 11 months. Serial luteal phase P levels were measured in 10 women experiencing regular menses over 39 cycles, and the majority of the cycles (79%) were determined to be ovulatory. These two studies both assessed relatively small numbers of women with PCOS and did not specifically analyze the effect of the duration of metformin treatment on the response rate. In a larger controlled study of 92 women with oligomenorrhea and polycystic ovary morphology, Fleming et al. (2) reported that ovulation frequency was significantly higher in the metformin-treated group versus the placebo group (23% vs. 13% respectively; $P<.01$).

Our study, to the best of our knowledge, is the first long-term (range of follow-up, 3–48 months) and large (n = 105) study to assess the influence of the duration of metformin treatment on menstrual cyclicity and response rate in PCOS. The study did not preselect women for metformin treatment on the basis of insulin sensitivity or other parameters, making the results generalizable to women with PCOS presenting for clinical care.

There are some limitations to our study. Because of the retrospective design, there is the potential for selection bias, although we attempted to reduce this likelihood by eliminating patients treated for <3 months. Another limitation is the lack of a nontreated control group. Furthermore, because it was not the practice of our physicians in the clinical setting to measure serum insulin levels, data on direct measurements of insulin sensitivity were not available.

In summary, these findings indicate that in a clinical practice setting, metformin is highly effective in normalizing menstrual cyclicity in women with PCOS. Treatment for at least 6 months leads to improvement of therapeutic efficacy over a shorter duration of treatment. Women who fail to respond to metformin tend to be more hyperandrogenic and dyslipidemic, reflecting perhaps more severe insulin resistance.

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