

## GYNECOLOGY

# Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial

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**OBJECTIVE:** To determine the effect of cinnamon on menstrual cyclicity and metabolic dysfunction in women with polycystic ovary syndrome (PCOS).

**STUDY DESIGN:** In a prospective, placebo controlled, double-blinded randomized trial, 45 women with PCOS were randomized (1:1) to receive cinnamon supplements (1.5 g/d) or placebo for 6 months. Menstrual cyclicity (average cycles/month) during the 6 months study period was compared between the 2 groups using the Mann-Whitney *U* test. Changes in menstrual cyclicity and insulin resistance between baseline and the 6 month study period were compared between the 2 groups using Wilcoxon signed rank tests.

**RESULTS:** The 45 women were randomized, 26 women completed 3 months of the study, and 17 women completed the entire 6 months of the study. During the 6 month intervention, menstrual cycles were more frequent in patients taking cinnamon compared with patients

taking placebo (median, 0.75; interquartile range, 0.5–0.83 vs median, 0.25; interquartile range, 0–0.54;  $P = .0085$ ; Mann-Whitney *U*). In patients taking cinnamon, menstrual cyclicity improved from baseline (+ 0.23 cycles/month 95% confidence interval, 0.099–0.36), yet did not improve for women taking placebo. ( $P = .0076$ , Wilcoxon signed rank). Samples ( $n = 5$ ) of serum from the luteal phase in different patients within the cinnamon group were thawed and ovulatory progesterone levels ( $>3$  ng/mL) confirmed. Luteal phase progesterone levels ( $>3$  ng/mL,  $n = 5$ ) confirmed ovulatory menses. Measures of insulin resistance or serum androgen levels did not change for either group.

**CONCLUSION:** These preliminary data suggest that cinnamon supplementation improves menstrual cyclicity and may be an effective treatment option for some women with PCOS.

**Key words:** cinnamon, PCOS, randomized controlled trial

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Mounting evidence has implicated insulin resistance and compensatory hyperinsulinemia in the pathogenesis of polycystic ovary syndrome (PCOS).<sup>1</sup> Women with PCOS have increased rates of insulin resistance

compared with controls, with absolute rates of insulin resistance as high as 65% in normal weight women and 95% in obese women.<sup>2,3</sup> Insulin resistance as well as hyperandrogenism in women with PCOS have been implicated in the dysfunction of the hypothalamic-pituitary-ovary axis, leading to anovulation and menstrual irregularity.<sup>4</sup>

Insulin sensitizing agents, such as metformin and thiazolidinediones, have been used successfully to treat women with PCOS.<sup>5</sup> Such agents have been shown to significantly reduce insulin resistance and androgen levels as well as some inflammatory markers, improve menstrual irregularity, and improve ovulatory function in some women with PCOS.<sup>6-8</sup> However, thiazolidinediones have multiple safety concerns and metformin, the most widely used drug in PCOS, is often poorly tolerated because of gastrointestinal side effects of nausea (61%), vomiting (30%), and diarrhea (65%).<sup>9,10</sup>

Cinnamon, a commonly used spice used since biblical times, has been found to have insulin sensitizing effects in both animal and human studies.<sup>11-13</sup> Although the mechanism is incompletely understood, cinnamon likely increases insulin sensitivity through intermediate metabolites acting at the cellular level.<sup>14</sup> In vitro studies and studies using animal models have shown that polyphenol polymers isolated from cinnamon increase insulin dependent glucose metabolism by activating the insulin receptor and altering glucose transport.<sup>15-17</sup>

Several groups have investigated the use of cinnamon in the treatment of diabetes. In a randomized, controlled clinical trial, daily intake of 1, 3, or 6 g of oral cinnamon (cinnamomum cassia) reduced serum glucose, triglycerides, LDL cholesterol, and total cholesterol in type II diabetes patients compared with placebo.<sup>12</sup> In another randomized, controlled trial, 3 g of oral cinnamon

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reduced fasting glucose in poorly controlled type II diabetes patients.<sup>18</sup>

Given the preliminary success of using cinnamon to treat insulin resistant diabetes and the established use of insulin sensitizing agents in the treatment of PCOS, cinnamon has been proposed as a possible alternative therapy for PCOS. In our own prospective placebo-controlled pilot study, cinnamon demonstrated significant reductions in fasting glucose and insulin resistance parameters after 8 weeks of oral cinnamon extract, 1 g per day.<sup>19</sup> However, the effects of cinnamon on symptoms and the metabolic dysfunction of PCOS have yet to be investigated in a large, randomized controlled trial. Accordingly, we applied to the United States Food and Drug Administration (FDA) to use cinnamon as an Investigational New Drug (IND) and have carried out a randomized, double-blinded, placebo-controlled trial investigating the effect of cinnamon on menstrual cyclicity in women with PCOS.

## MATERIALS AND METHODS

All study protocols and procedures were approved by the institutional review board of Columbia University. An application to use cinnamon supplements (Cinnulin PF; Integrity Nutraceuticals International, Spring Hill, TN) as an IND was submitted and accepted by the FDA (IND no. 110123). Regular reporting to the FDA and data safety monitoring board was performed as was required.

Patients aged 18-38 years meeting the Rotterdam criteria for polycystic ovary syndrome (oligomenorrhea or amenorrhea and either [1] clinical or biochemical evidence of hyperandrogenism or [2] ultrasound findings of polycystic ovaries) were recruited by print advertisement for participation in an international review board approved, registered, randomized, controlled clinical trial (NCT-01483118). Exclusion criteria were current pregnancy or lactation, current treatment of infertility, established diagnosis of diabetes mellitus, insulin sensitizing treatment within 3 months of study enrollment, hormonal treatment involving estrogen or progesterone

within 3 months of study enrollment, systemic, or inhaled corticosteroid use, known hypersensitivity to cinnamon, known seizure disorder, cardiovascular disease, or cerebrovascular disease. A wide range of body mass index (20-50) was included given the anticipated patient population and the suspected mechanism of action of cinnamon through metabolic pathways.

Patients meeting inclusion and exclusion criteria were offered study participation and informed consent was established. Patients were compensated for their time and effort at each visit, after randomization. Enrolled study patients were evaluated during the early follicular phase (day 3-7) after a spontaneous or induced menses. Height, weight, and vital signs were measured and recorded. Subcutaneous fat thickness was measured by transabdominal ultrasound. Antral follicle count and ovarian volume ( $\pi/6$  \*transverse diameter \*anterior-posterior diameter \* longitudinal diameter) were measured by transvaginal ultrasound. Fasting blood samples were obtained and a 2 hour 75 g glucose tolerance test was performed with phlebotomy 30, 60, and 120 minutes after glucose ingestion.

Subjects were randomized in a 1:1 fashion to receive either cinnamon supplements (125 mg capsule, 4 capsules 3x/day =1500 mg/day) or identically appearing 1.5 cm and 0.5 cm white placebo capsules (4 capsules, 3x/day) for the 6 month study period. The 1500 mg dose was chosen based on published clinical trials in diabetic patients and our own pilot study in patients with PCOS.<sup>11,16,17</sup> Both the study subjects and the investigators were blinded for the duration of the study, as drug and placebo samples were labeled in code by the manufacturer (Integrity Nutraceuticals International). All patients were advised to adhere to a balanced diet of 1800 calories per day and instructed to complete a daily menstrual calendar as well as an activity log. Compliance with diet and medications and interval progress was monitored with monthly visits with the investigators. The 2 hour 75 g glucose tolerance test was repeated at

the 3 month visit. A final visit at 6 months included height and weight measurements, vital signs, repeat trans-abdominal and transvaginal ultrasound, and repeat 75 g glucose tolerance test.

Serum levels of insulin, total testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), and sex-hormone binding globulin (SHBG) were measured with chemiluminescence assays using Immulite (Diagnostic Products Corporation, Los Angeles, CA). Baseline data from the study subjects (insulin resistance and androgen profiles) were compared with established controls from our previously published studies and reference values.<sup>20-23</sup>

The primary study outcome was menstrual cyclicity, approximated in the study by menstrual frequency, (number menses/number months observed) during the study period. Secondary outcomes were change in menstrual cyclicity from reported baseline cyclicity, change in insulin sensitivity indices (homeostasis model of insulin resistance [HOMA-IR], Quantitative Insulin Sensitivity Check Index [QUICK-I]), change in glucose response (area under the curve, trapezoidal method), change in serum androgen and SHBG levels, change in weight, change in subcutaneous fat measurements, and change in ovarian volume.

The Mann-Whitney *U* test was used to compare the number of menstrual cycles during the study period between the patients taking cinnamon and placebo. Wilcoxon signed-rank tests were used to compare all variables between baseline and at study completion in both the cinnamon and placebo groups. The target sample size was 40, powered to detect a 40% increase in menstrual cycle frequency with a type II error of 0.20 and a type I error of 0.05.

## RESULTS

Study enrollment began in Aug. 2011 and was terminated in Sept. 2012 because of expiration of the study drug and matched placebo in March 2013. Sixty-three women were screened and 45 patients were enrolled in the clinical trial (Figure 1). Twenty-three women were randomized to receive cinnamon and 22 women were randomized to

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