The physiological basis of complementary and alternative medicines for polycystic ovary syndrome

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Raja-Khan N, Stener-Victorin E, Wu X, Legro RS. The physiological basis of complementary and alternative medicines for polycystic ovary syndrome. Am J Physiol Endocrinol Metab 301: E1–E10, 2011. First published April 12, 2011; doi:10.1152/ajpendo.00667.2010.—Polycystic ovary syndrome (PCOS) is a common endocrine disorder that is characterized by chronic hyperandrogenic anovulation leading to symptoms of hirsutism, acne, irregular menses, and infertility. Multiple metabolic and cardiovascular risk factors are associated with PCOS, including insulin resistance, obesity, type 2 diabetes, hypertension, inflammation, and subclinical atherosclerosis. However, current treatments for PCOS are only moderately effective at controlling symptoms and preventing complications. This article describes how the physiological effects of major complementary and alternative medicine (CAM) treatments could reduce the severity of PCOS and its complications. Acupuncture reduces hyperandrogenism and improves menstrual frequency in PCOS. Acupuncture’s clinical effects are mediated via activation of somatic afferent nerves innervating the skin and muscle, which, via modulation of the activity in the somatic and autonomic nervous system, may modulate endocrine and metabolic functions in PCOS. Chinese herbal medicines and dietary supplements may also exert beneficial physiological effects in PCOS, but there is minimal evidence that these CAM treatments are safe and effective. Mindfulness has not been investigated in PCOS, but it has been shown to reduce psychological distress and exert positive effects on the central and autonomic nervous systems, hypothalamic-pituitary-adrenal axis, and immune system, leading to reductions in blood pressure, glucose, and inflammation. In conclusion, CAM treatments may have beneficial endocrine, cardiometabolic, and reproductive effects in PCOS. However, most studies of CAM treatments for PCOS are small, nonrandomized, or uncontrolled. Future well-designed studies are needed to further evaluate the safety, effectiveness, and mechanisms of CAM treatments for PCOS.

acupuncture; mindfulness meditation; herbs; dietary supplements; traditional Chinese medicine

POLYCYSTIC OVARY SYNDROME (PCOS), a common endocrine disorder that affects 5–10% of reproductive-age women, is characterized by chronic hyperandrogenic anovulation leading to symptoms of hirsutism, acne, irregular menses, and infertility (86). The exact etiology of PCOS remains unclear, but it is believed to result from complex interactions between genetic, behavioral, and environmental factors. Multiple metabolic and cardiovascular risk factors are associated with PCOS, including insulin resistance (IR), obesity, type 2 diabetes (DM-2), hypertension, dyslipidemia, inflammation, and subclinical cardiovascular disease (32, 62, 63, 87, 107). Anxiety, depression, and reduced quality of life are also common in PCOS (5, 19, 45, 107).

Current treatments for PCOS are only moderately effective at controlling symptoms and preventing complications. In fact, when 648 women were asked, “If your PCOS could be safely and effectively helped by something else besides fertility drugs or birth control pills, would that interest you?”, 99% responded yes (95). Although the prevalence of complementary and alternative medicine (CAM) used by women with PCOS is not known, a landmark study showed that one in three Americans use CAM (23). Recent studies suggest that several CAM treatments could be beneficial as an adjunct to conventional medical management of PCOS. This article describes how the physiological effects of CAM treatments could reduce the severity of PCOS and its endocrine, cardiometabolic, and reproductive complications.
Acupuncture

Acupuncture is a form of sensory stimulation in which thin needles are placed in the skin and muscles. It is of great importance to describe the needling “dose”, because the intensity, frequency, and type of stimulation, manual or electrical, with high or low frequency, and the interval between stimulations directly influence the kind of receptors activated and thus the therapeutic effect (114). Patients’ expectations may also influence the results, as acupuncture may have strong psychological effects (94).

The primary mechanism for acupuncture’s clinical effects is activation of somatic afferent nerves innervating the skin and muscles, which may modulate somatic and autonomic nervous system activity and endocrine and metabolic functions. The efficacy of acupuncture in treating pain and disease has been studied from a Western scientific perspective. Systematic reviews have concluded that there is no evidence for acupuncture point specificity and suggest that needles can be inserted anywhere in appropriate segments (80, 122). Here, we will use a neurophysiological approach to describe how acupuncture, specifically electro-acupuncture (EA), where needles are electrically stimulated, may work in women with PCOS, because it has good support from experimental and clinical studies (36, 79).

Etiology of PCOS. The etiology of PCOS is poorly understood (83). Ovarian hyperandrogenemia, the most consistent endocrine feature, probably plays a key role (30), but hyperinsulinemia/insulin resistance and abdominal obesity are also thought to be important (4). Whether hyperandrogenism results from the hyperinsulinemia of IR or vice versa is unclear (91). Moreover, neuroendocrine defects can contribute to persistently rapid luteinizing hormone (LH) pulsatility and increased amplitude, which further augment ovarian androgen production (7). In addition, PCOS women have high sympathetic nervous system activity compared with controls, and circulating testosterone is the strongest factor explaining the high activity (105). Furthermore, high activity in the sympathetic neurons innervating the ovaries precedes the development of ovarian cysts in rats (58), and women with PCOS may have increased ovarian nerve fiber density (37).

Clinical effects of acupuncture in PCOS. The clinical effect of acupuncture on menstrual dysfunction in PCOS has been evaluated in several case control studies (12, 29, 101, 117) and in one randomized controlled trial (RCT) (n = 84) (44). In the RCT, women were randomized in a 2:2:1 ratio to receive 14 treatments with low-frequency EA (n = 33) for 16 wk or physical exercise (n = 34) at least three times per week for 16 wk, or no intervention during the study period, which served as a control group (n = 17). This RCT demonstrated that low-frequency EA was superior to physical exercise and improved hyperandrogenism and menstrual frequency more effectively than no intervention (44). Whether the improved menstrual frequency reflected ovulation induction remains to be elucidated.

The effect of acupuncture (manual or electrical stimulation) on metabolic variables in women with PCOS has never been evaluated in clinical trials. Low-frequency EA, with repetitive muscle contraction, may activate physiological processes similar to those resulting from physical exercise and could influence metabolic variables. Experimental evidence is described below.

The effect of acupuncture on mental health and health-related quality of life in women with PCOS has not been evaluated in clinical trials. Acupuncture has been used to treat depressive disorders, but its effectiveness and safety are not well defined (124). Because women with PCOS are prone to develop symptoms of anxiety and depression and decreased health-related quality of life, this is an important area for exploration.

Placebo and limitations in acupuncture studies. Acupuncture treatment is associated with particularly potent placebo effects, and there are indications that acupuncture treatment may be associated with larger effects than pharmacological and other physical placebos (52, 53, 67). The characteristics of acupuncture treatment are relevant in the context of placebo effects, including frequent patient-practitioner contacts and the procedure of needling (51). Placebo effects result in true psychobiological events and exist in clinical practice (27).

Acupuncture studies are difficult to design for many reasons, including the variety of sham procedures, the number of acupuncture points used, the number and duration of acupuncture treatments, and differences in stimulation techniques (114). Studies involving acupuncture in which both the patient and the therapist are unaware of the treatment are practically impossible to conduct. Thus, many variables affect the outcome of an acupuncture study. The so called placebo-acupuncture needle (102) has been used in many trials, and most often it has similar effects to true acupuncture but is superior to no treatment if a no-treatment group is included. Thus, the placebo-acupuncture needle is not inert and may not be used as a sham (72). Instead, it is of importance to control for the increased amount of attention, and the control/comparison group should meet with a therapist the same amount of times as in the acupuncture group.

With this in mind, standardized study protocols to increase the validity of acupuncture studies by following the new revised STAndards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist in conjunction with CONSORT will improve critical appraisal, analysis, and replication of trials (73). Furthermore, given the uncertainties about physiological effects of sham controls and the question of enhanced placebo effects, it is crucial that direct, head-to-head comparisons of acupuncture and gold-standard treatment be conducted.

Physiological basis of acupuncture in PCOS: peripheral mechanisms. Insertion and manual or electrical stimulation of needles in skin and muscle activates Aα, Aβ, δ, and C fibers (49). In particular, activation of Aδ and C fibers may be essential for modulating autonomic nervous system activity (90). Manual and probably electrical stimulation causes release of neuuropeptides from peripheral nerve terminals into the area surrounding the needle, increasing blood flow (42). Low-frequency (2 Hz) EA also increases skeletal muscle glucose uptake (39). In insulin-resistant rats with dihydrotestosterone (DHT)-induced PCOS, peripheral insulin sensitivity is improved by low-frequency EA for 4–5 wk with three treatments per week (75) and normalized by five treatments per week (47). This normalization may reflect increased expression of soleus muscle glucose transporter (GLUT4) protein, including the plasma membrane of muscle cells (47). Moreover, there is a
dose-response relationship between the number of EA treatments and improvement in insulin sensitivity (74, 75). Similarly, in rats with prednisolone-induced IR, low-frequency EA acutely increases protein expression of insulin receptor substrate-1 and GLUT4 in skeletal muscle (65). Low-frequency EA improved insulin sensitivity in DM-2 \(db/db\) mice, and the effect was mediated, at least partly, via regulation of skeletal muscle Sirtuin-1 (SIRT1) and peroxisome proliferator-activated receptor-\(\gamma\) coactivator-1\(\alpha\) (PGC-1\(\alpha\)) (64). The increased peripheral blood flow and glucose uptake in skeletal muscle are most likely mediated by a reflex response from muscle twitches during manual or electrical stimulation, as the response is abolished after transection of somatic afferent nerve fibers (38) (Fig. 1).

**Segmental (spinal) mechanisms.** Needles in abdominal and leg muscles with somatic innervations corresponding to the sympathetic innervations of the ovaries, so-called segmental acupuncture points, may alter ovarian function by modulating sympathetic efferent activity (96, 98, 100). This is of particular interest since the PCOS ovary has been shown to have denser innervation (37) and high concentrations of nerve growth factor (NGF), a marker of sympathetic activity (20). Needles placed in the abdominal and hindlimb muscles of female rats and stimulated with low-frequency EA modulate the activity of ovarian sympathetic nerves, as reflected by increased ovarian blood flow (96, 98, 99). The response was demonstrated to be mediated by ovarian sympathetic nerves as a reflex response and was controlled by supraspinal pathways [i.e., central nervous system (CNS)] (96, 98). Further evidence that low-frequency EA modulates ovarian sympathetic nerve activity comes from studies in estradiol valerate-induced PCOS. Gene and protein expression of markers of sympathetic activity (\(\alpha_1\alpha\), \(\alpha_1\beta\), \(\alpha_1\delta\), and \(\beta_2\)-adrenergic receptors, NGF, the p75 neurotrophin receptor, and tyrosine hydroxylase) were normalized after 4 wk of low-frequency EA (76, 100). In rats with DHT-induced PCOS, ovarian morphology was improved by thrice weekly treatment for 4–5 wk, as reflected by a higher proportion of healthy antral follicles and a thinner theca interna cell layer than in untreated PCOS rats (74, 75). When treatment was increased to five times per week, low-frequency EA normalized estrus cyclicity, indicating a clear dose-response relationship (25). It is not known whether manual stimulation of acupuncture needles induces similar effects.

**Central mechanisms of acupuncture.** When needles are placed, the peripheral nervous system transfers signals to the brain, which contributes to the effect of acupuncture. Since the CNS regulates pituitary hormone release, acupuncture may also modulate endocrine and metabolic function.

Many brain areas, especially the hypothalamic nucleus, are involved in the effect of acupuncture. Acupuncture-induced release of CNS neuropeptides seems to be essential for inducing functional changes in organ systems (36). The central hypothalamic \(\beta\)-endorphin system is a key mediator of changes in autonomic functions, such as effects on the vasomotor center, which decreases sympathetic tone and is manifested as improved blood pressure regulation and decreased muscle sympathetic nerve activity (120). Both exercise and low-frequency EA increase hypothalamic \(\beta\)-endorphin secretion and decrease blood pressure and sympathetic nerve activity; these effects are reversed by \(\mu\)-opioid receptor antagonists (48). Interestingly, repeated low-frequency EA plus physical exercise significantly decrease high sympathetic nerve activity measured by microneurography in women with PCOS (97). Decreased sympathetic nerve activity, possibly mediated by modulation of hypothalamic \(\beta\)-endorphin secretion, may partly explain the decrease in circulating testosterone and improved menstrual frequency after low-frequency EA plus physical exercise in women with PCOS (44).

Hypothalamic \(\beta\)-endorphin interacts with the hypothalamic-pituitary-ovarian axis by exerting a tonic inhibitory effect on
the gonadotropin-releasing hormone (GnRH) pulse generator and on pituitary LH release (46). In PCOS, growing evidence suggests that the opioid system is dysregulated both centrally and peripherally, with complex interactions (24). Indeed, opioid receptor antagonists improve menstrual cyclicity, induce ovulation, and decrease testosterone, insulin, and LH levels and the LH/FSH ratio (1, 15, 28). Acupuncture might affect the hypothalamic-pituitary-ovarian axis by modulating central β-endorphin production and secretion, thereby influencing release of hypothalamic GnRH and pituitary secretion of gonadotropins, as shown by the decrease in LH/FSH ratio after low-frequency EA (101). Furthermore, in rats with DHT-induced PCOS, five low-frequency EA treatments per week for 4–5 wk restored high hypothalamic androgen receptor and GnRH protein expression, which may help explain the beneficial neuroendocrine effects of low-frequency EA in women with PCOS (25).

β-Endorphin is also released into peripheral blood from the hypothalamus via the anterior pituitary, a process regulated by CRF. Circulating β-endorphin is thought to be related to the hyperinsulinemic response (70). It may also decrease hyperinsulinemia by lowering high concentrations of circulating β-endorphin (101). Interestingly, low-frequency EA lowers high circulating β-endorphin concentrations in women with PCOS and may decrease hyperinsulinemia and increase insulin clearance or insulin sensitivity (12, 101).

In sum, clinical and experimental evidence indicates that acupuncture with electrical muscle stimulation may be a suitable alternative or complement to improving endocrine and reproductive function in women with PCOS without adverse side effects. More experimental mechanistic studies and RCTs to further explore the use of acupuncture to treat PCOS-related symptoms are warranted.

**Chinese Herbal Medicine**

Chinese herbal medicine (CHM) is an integral part of traditional Chinese medicine (TCM). In China today, TCM is often administered as a complement to Western medicine. While TCM traces its roots back thousands of years, it rests, from the view of evidence-based medicine, more on a philosophy than a science. Much of the central philosophy involves maintaining the balanced flow of life energy (qi). TCM views organ systems as contributing to mind-body states and tries to address imbalances of these organ systems. TCM views PCOS as linked to disorders of the kidneys, liver, and spleen. Reproductive abnormalities, especially anovulation, are believed to be linked to the kidney, and a deficit in kidney is viewed as the primary problem in PCOS (82, 110).

Traditionally, CHMs are combined in varying preparations. Although some preparations are regulated by the government, there remains concern about quality control of individual formulations, given the variation in plant quality from harvest to harvest, and concerns about harmful supplements or byproducts of preparation such as heavy metals, herbicides, pesticides, microorganisms, mycotoxins, insects, pharmaceuticals, etc. (6, 68). The FDA has published guidelines to ensure better quality control of manufactured products from plants, but many of these products fall outside of regulation by the FDA, as they are not pharmaceuticals. CHMs also include many animal byproducts that we will not discuss in detail in this review. For example, a common preparation used to induce ovulation in women with PCOS is Di Long (Earth Dragon), which is made from abdominal extracts of the red earthworm Lumbricus rubellus.

**Safety and efficacy of CHMs.** Unfortunately, there is minimal evidence that CHMs are safe and efficacious. Most of the trials have been small and thus inadequately powered to detect true differences. Most, not surprisingly, have been conducted mainly in Chinese populations and published in Chinese and thus are not easily accessible. The studies have also tested a large number of varying preparations (most containing multiple components), and thus there has been little to no replication for individual preparations. Above all, the studies have been of poor methodological quality without adherence to CONSORT guidelines.

This is well illustrated by systematic reviews of CHM in subfertile women with PCOS (123) and patients with impaired glucose tolerance (IGT) (34) and DM-2 (68), disorders related to PCOS because of the common underlying link of IR (Table 1).

Here, we also review the evidence for CHM in IGT and DM-2 because women with PCOS are at markedly increased risk for both IGT and DM-2 due to IR (65). Furthermore, these disorders of glucose dysregulation may represent later stages in the pathophysiological progression of PCOS. Finally, many drugs used to prevent or treat PCOS have been borrowed from DM-2, most notably metformin, but also the thiazolidinediones, acarbose, but also newer agents such as incretin mimetics such as exenatide. Similarly, many of the CHMs used to treat DM-2 may be useful for PCOS. However, the evidence for the benefit of CHM in all three disorders is weak (Table 1).

There are the fewest articles for PCOS, which is perhaps understandable from a public health perspective, as IGT and DM-2 are more prevalent than PCOS. The large drop-off from published articles to those meeting the minimum quality standard for a systematic review is staggering. None of the studies documented allocation concealment (the method by which the order of treatment assignment was generated and implemented in the study) or blinding, none of the studies used an intention to treat method analysis, a standard method to account for drop-out in a randomized trial (123).

The authors of the review of CHM in PCOS (123) did note that in two studies where multiple formulations of Chinese herbs were given as adjuvant therapy to clomiphene, there was a significantly increased odds of pregnancy with CHM (OR 2.97, 95% CI 1.71 to 5.17) (123). The reviews (34, 68, 123) share a common theme, a hint of efficacy clouded by poor methodology and lack of replication. But all reviews were eager to see larger better designed studies carried out.

There are multiple hurdles to adapting CHM into Western medicine. One is the lack of scientific justification from a hypothesis-driven perspective for the use of these medications. Many herbs contain multiple active substances, and combinations are exponentially more problematic for determining what is doing what to what. Much research currently is focusing on compound analysis through such technologies as high-performance liquid chromatography-mass spectrometry to identify specific bioactive agents.

**Physiological mechanisms of CHMs.** Currently, the physiological mechanisms for efficacy of most CHMs are unknown in PCOS. Table 2 lists several CHMs used in PCOS and their
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Table 1. List of systematic reviews of CHM for treatment of PCOS and disorders of glucose metabolism including type 2 diabetes

<table>
<thead>
<tr>
<th>Topic</th>
<th>Total No. of Studies Retrieved</th>
<th>Total Studies Included in Cochrane Review</th>
<th>Total No. of Studies in Chinese</th>
<th>Total No. of Subjects in Included Studies</th>
<th>Total No. of Preparations Tested in Trials</th>
<th>Main Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subfertile PCOS (123)</td>
<td>267</td>
<td>4</td>
<td>4</td>
<td>334</td>
<td>6</td>
<td>Limited evidence that addition of CHM to clomiphene is associated with improved clinical pregnancy outcomes and no other evidence of any other effect. Methodology of RCTs was not adequately reported. Some positive evidence favors CHM for treatment of IGT or IFG. Limited by the following factors: lack of trials that tested the same herbal medicine, lack of details on cointerventions, unclear methods of randomization, poor reporting, and other risks of bias.</td>
</tr>
<tr>
<td>Impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (34)</td>
<td>1,926</td>
<td>16</td>
<td>15</td>
<td>1,391</td>
<td>15</td>
<td>Some positive evidence favors CHM for treatment of IGT or IFG. Limited by the following factors: lack of trials that tested the same herbal medicine, lack of details on cointerventions, unclear methods of randomization, poor reporting, and other risks of bias.</td>
</tr>
<tr>
<td>Type 2 diabetes (68)</td>
<td>713</td>
<td>66</td>
<td>61</td>
<td>8,302</td>
<td>69</td>
<td>Some herbal medicines show hypoglycemic effect in type 2 diabetes. However, these findings are limited by low methodological quality, small sample size, and limited number of trials.</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovary syndrome; CHM, Chinese herbal medicine; RCT, randomized controlled trial. Nos. in parentheses are references.

A proposed mechanism of action. Many may have selective estrogenic effects and function like clomiphene to induce ovulation. Risks, however, must be carefully determined, and these have not been well delineated. Gancao or licorice, given chronically or in excess, can cause an acquired form of apparent mineralocorticoid excess, as it is a potent inhibitor of 11β-hydroxysteroid dehydrogenase. This enzyme inactivates cortisol to cortisone, and decreased inactivation, especially in the kidney, can lead to excess cortisol cross-reacting with the mineralocorticoid receptor, which induces fluid retention, hypokalemia, and hypertension (66). In addition, CHMs may interfere with the metabolism of other drugs used to treat PCOS. For example, plantain has been proposed to interfere with many commonly prescribed medications such as digitoxin and tricyclic antidepressants, although at least one study shows no clinical interactions (17).

Mechanisms of action should be explored in cell culture and animal models by basic scientists. For example, Ocimum basilicum has been found in an in vitro tissue model to inhibit intestinal glucose absorption and stimulate glucose uptake in fibroblasts and adipocytes (59). Furthermore, in a streptozotocin-induced diabetes mouse model, it lowers plasma glucose and triglycerides and improves insulin levels (119). Other CHMs, such as Radix notoginseng, have been found to have similar antidiabetic effects in mouse models, improving not only glucose tolerance and insulin action in a dose-response fashion but also ameliorating obesity (13). Similarly, Salvia miltiorrhiza Bunge has been shown to significantly improve glucose tolerance in a prenatally androgenized rat model of PCOS and to favorably impact insulin signaling in treated animals (118). Berberine, a component of Rhizoma coptidis, has been shown to improve glucose uptake and insulin action in human thecal cells with dexamethasone-induced insulin resistance (125). These favorable changes in glucose metabolism have also been shown to favorably alter sex steroid feedback or production, ameliorating hyperandrogenism in these models (22, 125). Additionally, antioxidant activity has been noted in vitro for a number of these substances (61, 116).

Furthermore, extensive investigation of promising drugs should be established in preliminary studies, first exploring

Table 2. Partial list of CHMs used to treat PCOS, their proposed mechanisms of action, and their reported side effects

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Chinese Name</th>
<th>Latin Name</th>
<th>English Name</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve insulin sensitivity</td>
<td>Baihao</td>
<td>Radix paeonie Alba</td>
<td>White peony root</td>
<td>Uterine contractions, interfere with blood clotting</td>
</tr>
<tr>
<td></td>
<td>Danggui</td>
<td>Radix angelicae Sinensis</td>
<td>Angelica</td>
<td>Uterine contractions</td>
</tr>
<tr>
<td></td>
<td>Danshen</td>
<td>Salvia miltiorrhiza Bunge</td>
<td>Red sage</td>
<td>May interact and potentiate effects of warfarin</td>
</tr>
<tr>
<td>Induce ovulation (through estrogenic effects)</td>
<td>Huang Lian Luole</td>
<td>Rhizoma copidis Ocimum basilicum</td>
<td>Goldenthread Basil</td>
<td>Hypertension, respiratory failure, paresthesias</td>
</tr>
<tr>
<td></td>
<td>Sanqi</td>
<td>Radix no-toginseng</td>
<td>Panax pseudoginseng</td>
<td>Contains a chemical, estragole, which has caused liver cancer in mice</td>
</tr>
<tr>
<td></td>
<td>Zelan</td>
<td>Herba lycopi</td>
<td>Bugleweed</td>
<td>Dry mouth, flushed skin, nervousness, sleep problems, nausea, and vomiting</td>
</tr>
<tr>
<td></td>
<td>Zexie</td>
<td>Rhizoma alismatis</td>
<td>Water plantain</td>
<td>Enlarged thyroid gland, hypoglycemia</td>
</tr>
<tr>
<td>Inhibit androgen synthesis</td>
<td>Gancao</td>
<td>Radix glycytthiae</td>
<td>Licorice</td>
<td>Fresh rootstock may be poisonous</td>
</tr>
</tbody>
</table>

Hypersensitivity, fluid retention, hypokalemia, exacerbate kidney disease.
safety and secondarily exploring proof of concept through larger dose ranging studies. This is certainly the FDA model for new drugs; i.e., begin with Phase I studies, progress to dose ranging and further safety Phase II studies, and finally choose a dose and perform a large-scale, adequately powered and designed Phase III efficacy study. Second, there remains, at least in the US, a great gulf between practitioners of TCM and allopathic physicians and a general skepticism of the Weltanschauung of the other. Along these lines, there is a lack of adequately trained investigators who are familiar both with CHM and with the design and implementation of RCTs. This latter element is especially lacking in China, where most of these trials are conducted, as the systematic reviews document.

A group of international authors has recognized the unique challenges of RCTs of CHMs and made the following summary recommendations to improve the quality of these trials by ensuring the stability, consistency, and purity of CHMs. These suggested guidelines, replicated here, are a positive step toward the exploration of CHMs for the treatment of PCOS and related disorders. At present, their potential is untapped, although this represents a tremendous opportunity for researchers on both sides of the ocean.

### Dietary Supplements

Several dietary supplements may have beneficial effects on PCOS. However, most studies are small or uncontrolled. Therefore, larger, better-designed studies are needed to further evaluate the risks and benefits of these supplements in PCOS. In addition, it is important to note that the supplements discussed here are not FDA approved for the treatment of PCOS.

**Vitamin D.** Accumulating evidence suggests that vitamin D deficiency may be a causal factor in the pathogenesis of IR and the metabolic syndrome in PCOS (35). Furthermore, 25-hydroxyvitamin D levels are closely associated with impaired β-cell function, IGT, and the metabolic syndrome in PCOS women (113). Two small, uncontrolled studies demonstrate that vitamin D may improve IR and lipid profiles in PCOS patients (56, 92). One of these studies demonstrated a significant reduction in homeostatic model assessment of insulin resistance (HOMA-IR) 3 wk after a single oral vitamin D3 dose of 300,000 IU in 11 obese, insulin-resistant women with PCOS (56, 92). Moreover, vitamin D supplementation may also improve anovulation in PCOS. A pilot RCT of 60 infertile PCOS patients showed that the number of dominant follicles (≥14 mm) during 2–3 mo of follow-up was higher in the calcium (1,000 mg/day) plus vitamin D (400 IU/d) plus metformin (1,500 mg/day) group than in the calcium + vitamin D-only group or the metformin-only group (88).

**Vitamin B12 and folate.** Two recent studies suggest that B vitamins may be important in PCOS. In the first study, IR, obesity, and elevated homocysteine were associated with lower serum vitamin B12 concentrations in PCOS patients (55). The second study was a nonrandomized, placebo-controlled, double-blind trial that demonstrated that supplementation with folate (400 μg daily) for 6 mo increases the beneficial effect of metformin on the vascular endothelium in women with PCOS (84). However, the mechanisms are still unclear.

**Green tea and spearmint tea.** Tea, next only to water, is the most popularly consumed beverage in the world, with a per capita consumption of 120 ml/day (78). Green tea has been shown to exert beneficial effects on glucose and lipid metabolism (11, 21) and the hormonal system (26, 50) in rats and humans, which are all very relevant in the management of PCOS patients. In addition, herbal tea reduces body weight and induced ovulation in androgen-sterilized rats (103). However, there are only two RCTs of herbal tea in PCOS, one using green tea (10) and the other spearmint tea (33).

The principal component of green tea, (−)-epigallocatechin-3-gallate (EGCG), significantly reduced body weight and circulating testosterone, estradiol, leptin, insulin, IGF-I, LH, glucose, cholesterol, and triglyceride in Sprague-Dawley rats and lean and obese Zucker rats (50). In vitro studies demonstrate that green tea extract and EGCG inhibit basal and stimulated testosterone production in rat Leydig cells. The mechanisms underlying the effects of EGCG involve the in vitro inhibition of the PKA/PKC signaling pathways as well as the inhibition of P-450 side-chain cleavage enzyme and 17β-hydroxysteroid dehydrogenase function during testicular steroidogenesis (26).

In an RCT of 34 obese Chinese women with PCOS, the body weight of the green tea capsule group (540 mg EGCG/day) decreased by a nonsignificant 2.4% after treatment, whereas the body weight, body mass index (BMI), and body fat content of the control group were significantly higher after 3 mo (10). However, there were no significant differences in glucose, lipid metabolism, or any of the hormone levels between the two groups. The lack of a positive finding in this study may be due to an inadequate dose of green tea and the small sample size of the study. Furthermore, the response to EGCG may be greater in other ethnic groups, especially those groups who do not already have a strong habit of taking tea in their daily lives (121).

In regard to spearmint tea, an RCT of 41 PCOS women showed that spearmint tea twice a day for 1 mo significantly decreased free and total testosterone levels, improved patients’ subjective assessments of their hirsutism, and increased LH and FSH compared with a placebo herbal tea (33). Further studies are needed to confirm these findings and further elucidate the mechanisms underlying the antiandrogenic effects of spearmint tea.

**Cinnamon extract.** Cinnamon extract (a traditional herb) has been shown to potentiate the insulin effect through upregulation of glucose uptake in cultured adipocytes (3, 8, 43). Cinnamon extract also improves insulin action via increasing glucose uptake in vivo, as it has been shown to enhance the insulin-signaling pathway in skeletal muscle in rats (85). An RCT of 15 women with PCOS showed significant reductions in IR in the cinnamon group (333 mg of cinnamon extract, 3 times a day) but not in the placebo group (111).

**ω-3 and other polyunsaturated fatty acids.** A small RCT of 25 PCOS women demonstrated that dietary supplementation with ω-3 fatty acid 4 g/day (4 × 1,000-mg capsules of 56% docosahexaenoic acid and 27% eicosapentaenoic acid; Ocean Nutrition, Halifax, NS, Canada) for 8 wk has beneficial effects on liver fat content and other cardiovascular risk factors in women with PCOS (16). Another small study, of 17 women with PCOS, showed that increased dietary polyunsaturated fatty acid (PUFA) intake from walnuts (48 g walnuts per 800 kcal energy intake) for 3 mo increased glucose levels in women with PCOS (54). Forty-eight grams of walnuts contain 311 kcal (70 kcal from 30 g fat, 28 kcal from 7 g protein, and 36 kcal from 9 g carbohydrates) and provide 19 g of linolenic acid and...
3.3 g of α-linolenic acid. Further studies are needed to determine the risks and benefits of ω-3 fatty acids and other PUFAs in PCOS.

Qi Gong and Tai Chi

Exercise is an important component of a healthy lifestyle, and it reduces metabolic and reproductive disturbances in PCOS. Qi gong and Tai chi are the two most popular Chinese medical exercises worldwide. Qi gong may be beneficial for individuals with DM-2 or metabolic syndrome, for its favorable effects on hemoglobin (Hb) A1c, glucose levels, and insulin sensitivity, reported by several RCTs (69, 104, 109). Tai chi has been shown to have similar energy expenditure to other moderate-intensity activities, such as walking at a speed of 6 km/h (2). It also has favorable effects on glucose control, lipid profile, and anxiety in patients with DM-2 (41, 108, 112). Therefore, Qi gong and Tai chi may be effective adjunct treatments for PCOS women. However, to date no studies have evaluated the effects of Qi gong or Tai chi in PCOS.

Mindfulness Meditation

Mindfulness, a component of ancient meditative practices such as Vipassana meditation and Zen meditation, is increasingly being applied to Western medicine to enhance psychological health and overall well-being (14, 71). In contemporary Western psychology, mindfulness has been described as the awareness that emerges through intentionally paying attention to one’s present thoughts, emotions, and bodily sensations moment to moment in a nonjudgmental manner (93). Mindfulness has not been investigated in women with PCOS; however, studies in non-PCOS populations, including patients with DM-2 (89), suggest that mindfulness has psychological and physiological effects that could be beneficial in PCOS. Mindfulness-based stress reduction (MBSR), the most researched mindfulness-based program, reduces psychological distress (71) and may also reduce blood pressure, glucose, and inflammation (9, 77, 89, 115). These physiological effects appear to be mediated by changes in brain activity (18, 31) and structure (40, 60) leading to improvements in the autonomic nervous system (57, 81, 106) and hypothalamic-pituitary-adrenal (HPA) axis (9, 77, 115). It is hypothesized that these beneficial effects of mindfulness might ultimately lower the risk for diabetes and cardiovascular disease in PCOS. However, most of the evidence comes from small, uncontrolled, nonrandomized studies in non-PCOS populations. Therefore, well-designed RCTs of mindfulness in women with PCOS are needed before definitive conclusions can be drawn regarding the effects and mechanisms of mindfulness in PCOS.

Conclusions

In conclusion, several CAM treatments may have beneficial endocrine, cardiometabolic, and reproductive effects in women with PCOS. However, most studies are small, nonrandomized, or uncontrolled. Therefore, larger, well-designed RCTs are needed to further evaluate the safety, effectiveness, and mechanisms of CAM treatments for PCOS.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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