Acupuncture in Polycystic Ovary Syndrome: Current Experimental and Clinical Evidence

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Polycystic ovary syndrome (PCOS), the most common female endocrinopathy, is associated with hyperandrogenism, ovulatory dysfunction and obesity (1). PCOS increases the risk of metabolic disturbances such as hyperinsulinaemia and insulin resistance, which can lead to type 2 diabetes, hypertension and an increased likelihood of developing cardiovascular risk factors and impaired mental health later in life. Despite extensive research, little is known about the aetiology of PCOS. The syndrome is associated with peripheral and central factors that influence sympathetic nerve activity. Thus, the sympathetic nervous system may be an important factor in the development and maintenance of PCOS. Many women with PCOS require prolonged treatment. Current pharmacological approaches are effective but have adverse effects. Therefore, nonpharmacological treatment strategies need to be evaluated. Clearly, acupuncture can affect PCOS via modulation of endogenous regulatory systems, including the sympathetic nervous system, the endocrine and the neuroendocrine system. Experimental observations in rat models of steroid-induced polycystic ovaries and clinical data from studies in women with PCOS suggest that acupuncture exert long-lasting beneficial effects on metabolic and endocrine systems and ovulation.

Key words: acupuncture, insulin resistance, metabolic syndrome, obesity, opioids, ovulation, physical exercise, polycystic ovary syndrome, sympathetic nerve activity.

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increases ovarian androgen production and further exacerbates symptoms of PCOS (11). Adiposity is also important in the pathogenesis of PCOS (1), as shown by improved menstrual regularity after weight reduction (12–14). Visceral fat, which is metabolically more active than subcutaneous adipose tissue, tends to accumulate in women with PCOS (15) and the increased fat mass and central adiposity are related to hyperinsulinaemia from prepuberty to postmenarche (16). In line with these observations, PCOS is associated with two strong predictors of insulin resistance: enlarged adipocytes and reduced lipolytic activity (17). Thus, lipid mobilisation, a process tightly regulated by insulin and the sympathetic nervous system, appears to be disturbed in women with PCOS.

Furthermore, PCOS appears to have a genetic basis, but the genes involved are unknown. Likely candidates include genes that regulate ovarian steroidogenesis or influence body mass index and adiposity (18). The symptoms and severity of PCOS vary, suggesting subpopulations among women with the syndrome.

The disturbances in PCOS have been attributed to defects in different organ systems. These include androgen synthesis defects that enhance ovarian androgen production and alter cortisol metabolism resulting in enhanced adrenal androgen production, neuroendocrine defects with exaggerated luteinising hormone (LH) pulsatility and defects in insulin action and secretion leading to hyperinsulinaemia and insulin resistance (2) (Fig. 1).

Sympathetic nervous system in the pathogenesis of polycystic ovary syndrome

The primary aetiology of this complex disease remains a hen-and-egg mystery; thus, the sympathetic nervous system may be an important aetiological factor, as described below. PCOS is associated with peripheral and central factors that influence sympathetic nerve activity. The central β-endorphin system exerts tonic inhibitory control on the gonadotrophin-releasing hormone (GnRH) pulse generator, on pituitary LH release and modulates sympathetic tone. Absolute LH augmentation is dependent on baseline LH levels and may account for difference in LH responsiveness in women with PCOS. LH responses to GnRH and LH pulse amplitude do not correlate with LH pulse frequency, suggesting the involvement of other factors, such as GnRH together with androgens and/or body mass index, to account for the increased LH release in PCOS (19). Tonic augmented release of LH may be caused by diminished or exaggerated β-endorphin and dopaminergic control of GnRH release (20, 21).

High plasma β-endorphin levels may contribute to PCOS and seem to be related to hyperinsulinaemia (22) and stress (23). Increased sympathetic nerve activity is the most common risk factor for cardiovascular disease and mortality (24, 25), and women with PCOS are more prone to develop hypertension and other cardiovascular disturbances (26).

Obesity, particularly abdominal obesity, and insulin resistance are risk factors for hypertension and cardiovascular disease in women.

Fig. 1. Abnormalities in polycystic ovary syndrome (PCOS) have been attributed to primary defects in the hypothalamic-pituitary-adrenal (HPA) axis, the ovarian microenvironment, the adrenal gland, and the insulin/insulin growth factor-1 metabolic regulatory system. Furthermore, the potential contribution of the sympathetic nervous system to PCOS has been suggested by several observations because the syndrome is associated with both peripheral and central factors that influence sympathetic nerve activity. CNS, Central nervous system; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; HT, hypothalamus; P, pituitary; SHBG, sex hormone binding globulin.
with PCOS (27). In patients with congestive heart failure, visceral obesity appears to be the most important determinant of excessive sympathetic activation (28). Increased sympathetic nerve activity may also be linked to hyperandrogenism (29, 30), hyperinsulinaemia (31) and hypertension (32). Furthermore, growth hormone (GH) and insulin growth factor-1 (IGF-1) play central roles in regulating sympathetic nerve activity. A recent study found disturbances in the somatotrophic axis (GH/IGF-1) in PCOS (33). Sympathetic nervous system involvement is further supported by the greater density of catecholaminergic nerve fibres in polycystic ovaries (PCO) (34, 35). Increased ovarian sympathetic nerve activity might contribute to PCOS by stimulating androgen secretion (36). This would explain why ovarian wedge resection or laparoscopic laser cauterisation (37), which likely disrupt ovarian sympathetic innervation, increase ovulatory responses in women with PCOS. The importance of the sympathetic nervous system in PCOS pathophysiology needs to be investigated further. Table 1 summaries the relation between sympathetic nervous system and PCOS.

### Experimental evidence of involvement of sympathetic nervous system in polycystic ovaries

Validated animal models are valuable for therapeutic screening, preclinical trials and studying the pathogenesis of complex reproductive disorders such as PCOS. Observations in prenatally androgenised rhesus monkeys and sheep (38, 39) suggest that androgen hypersecretion from the ovaries or adrenals, most likely before puberty, can cause clinical and biochemical features of human PCOS.

In rats, a single i.m. injection of oestradiol valerate (EV) induces an anovulatory state with endocrinological and morphological characteristics of human PCOS (40); ovarian sympathetic nerve activity is higher in this model than in normal rats (41–43). The sympathetic nerves appear to be involved in controlling ovarian secretory activity and are important regulators of ovarian function because noradrenaline and vasoactive intestinal peptide potently stimulate steroid secretion (44). EV-induced PCO in rats is associated with increased peripheral sympathetic outflow, as demonstrated by increases in noradrenaline release and ovarian noradrenaline content and a reduced number of $\beta_2$-adrenoceptors in the ovarian compartment receiving catecholaminergic innervation (41, 42). The increased ovarian sympathetic nerve activity may reflect augmented ovarian production of nerve growth factor (NGF), a target-derived neuropeptide (43, 45, 46). Further, $\alpha_1$-adrenoceptor subtypes are up-regulated in the ovaries of PCO rats (47), which further supports the involvement of the sympathetic nervous system in the regulation of ovarian function.

However, programming with EV in adult rats does not cause the metabolic disturbances seen in PCOS (48) and few rat models have focused on the metabolic disturbances that are a major feature of human PCOS.

Female rats exposed to testosterone (49), or the aromatase inhibitor letrozole (50), develop cystic follicles and endocrine features similar to human PCOS but it is unclear whether they develop metabolic disturbances.

Because PCOS symptoms usually develop during early puberty, when androgen production commences, we assessed the contribution of androgens to PCOS by evaluating the effects of prepubertal administration of dihydrotestosterone (DHT), a non-aromatisable androgen, or letrozole in rats during adulthood (51). Adult DHT rats presented irregular cycles and polycystic ovaries characterised by cysts formed from atretic follicles with a diminished granulosa layer. They also displayed metabolic disturbances, including increased body weight, body fat, mesenteric adipocyte size and leptin levels, as well as insulin resistance. All letrozole rats became anovulatory with polycystic ovaries, including structural changes strikingly similar to those in human PCOS, although they were not insulin resistant or obese. Thus, the letrozole model was concluded to be suitable for studies of the ovarian features of PCOS whereas the DHT model was suitable for studies of the ovarian and metabolic features (51). Evidence is required to demonstrate whether these new models are related to increased sympathetic nerve activity. Hypothetically, sympathetic nerve activity is increased in the ovaries and in adipose tissue.

### Acupuncture in polycystic ovary syndrome

Many women with PCOS require prolonged treatment. Pharmacological approaches are effective but have adverse effects. First-line therapy in PCOS is often oral contraceptives, which reduce hirsutism and acne but adversely affect glucose tolerance, coagulability and fertility (52). Therefore, treatment strategies such as acupuncture need to be evaluated in PCOS. Acupuncture, a treatment that dates back 3000–5000 years, is an integral part of traditional Chinese medicine and has become more established in Western medicine as a complement or alternative to conventional therapies.

What is the physiological basis for using acupuncture in PCOS? Intramuscular needle insertion cause a particular pattern of afferent activity in peripheral nerves. Depending on the intensity, stimulation of the acupuncture needles activate muscle afferents to the spinal cord and the central nervous system (53). In electro-acupuncture (EA), low-frequency (1–15 Hz) electrical stimulation excite ergoreceptors in the muscles (54), which are physiologically activated during muscle contractions. Low-frequency EA cause release of a

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**Table 1. Clinical Signs and Symptoms in Polycystic Ovary Syndrome (PCOS) Associated With Increased Activity in the Sympathetic Nervous System.**

<table>
<thead>
<tr>
<th>Signs and symptoms in PCOS</th>
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<tr>
<td>Hyperandrogenism</td>
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<tr>
<td>Hypersecretion of LH → anovulation</td>
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<tr>
<td>Increase in ovarian catecholaminergic nerve fibres</td>
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<tr>
<td>Visceral obesity</td>
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<tr>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Disturbed GH/IGF-1 axis</td>
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<td>Psychological stress</td>
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LH, Luteinising hormone; GH, growth hormone; IGF, insulin growth factor.
large number of neuropeptides, serotonin, endogenous opioids and oxytocin, which appears to be essential for inducing functional changes in different organ systems (55). Of particular interest is \( \beta \)-endorphin, an endogenous opioid with high affinity for the \( \mu \)-receptor (56).

\( \beta \)-endorphin is produced and released from hypothalamic nucleus, the nucleus arcuatus and the nucleus tractus solitarius in the brain steam. This central hypothalamic \( \beta \)-endorphin system appears to be a key mediator of changes in autonomic functions after acupuncture (55). The changes are probably caused by inhibition of the vasomotor centre, which decrease sympathetic tone and blood pressure (55) (Fig. 2). \( \beta \)-endorphin is also released into peripheral blood from the hypothalamus via the anterior pituitary (57), a process regulated by corticotrophin-releasing factor (CRF), which is secreted from the paraventricular nucleus of the hypothalamus. CRF promotes the release of \( \beta \)-endorphin, adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone in equimolar amounts by stimulating the synthesis of their precursor, pro-opiomelanocortin. \( \beta \)-endorphin in plasma is thought to be related to the hyperinsulinemic response (22) and stress (23). Stress increases hypothalamic-pituitary-adrenal (HPA) axis activity and decreases reproductive functions. Thus, hormones of the HPA axis are closely related to those of the hypothalamic-pituitary-gonadal (HPG) axis. CRF, ACTH, \( \beta \)-endorphin and adrenal corticosteroids modulate the effects of stress on reproductive functions (58). Acupuncture affects the HPA axis by decreasing cortisol concentrations (59) and the HPG axis by modulating central and peripheral \( \beta \)-endorphin production and secretion, thereby influencing the release of hypothalamic GnRH and pituitary secretion of gonadotrophin (60–63). The central and peripheral \( \beta \)-endorphin systems operate independently, but both can be stimulated by afferent nerve activity (i.e. manual acupuncture and EA) (55).

Acupuncture modulates spinal reflexes (64). In our experimental rat studies, low-frequency EA increased ovarian blood flow. The

![Ergoreceptor](attachment:image1.png)

**Fig. 2.** A hypothetical model of the effects of low-frequency electro-acupuncture (EA) in polycystic ovary syndrome (PCOS). Needle insertion to the skin and muscle excites ergoreceptors and cause afferent activity in \( A\delta \)-, and \( C \)-fibres. Needles placed and stimulated in the same somatic innervation area as the ovary decrease sympathetic nerve activity, which leads to decreased secretion and the release of ovarian androgens. In parallel, the activity of higher control systems is modulated by the release of opioids, in particular \( \beta \)-endorphin (\( \beta \)-END) that induces functional changes in different organ systems. In women with PCOS, we suggest an increased sympathetic nerve activity and an increased \( \beta \)-END production/release. Low-frequency EA decreases the central \( \beta \)-END, providing decreased sympathetic tone and decreased LH and release of \( \beta \)-END into the bloodstream. Low-frequency EA may further decrease hypothalamic-pituitary-adrenal (HPA) axis activity by inhibiting release of corticotrophin-releasing factor (CRF), causing decreased adrenocorticotropic hormone (ACTH) release from the pituitary gland and decreased cortisol/dehydroepiandrosterone (sulfat) [DHEA (S)] release from the adrenal cortex and a decrease in sympathetic adrenal (SA) axis activity. The adrenal medulla will then decrease noradrenaline and adrenaline secretion. A, Adrenal gland; CNS, central nervous system; FSH, follicle stimulating hormone; HT, hypothalamus; LH; luteinising hormone; P, pituitary; VMC, vasomotor centre.
needles were placed in the abdomen and hind limb, which have the same somatic innervation as the ovaries and uterus (65, 66). The response was mediated via ovarian sympathetic nerves as a reflex response and controlled by supraspinal pathways (65, 66).

Whether the release of β-endorphin is increased or possibly decreased in women with PCOS is not fully understood. However, opioid antagonist treatment has been shown to improve PCOS related symptoms via regulation of insulin and/or LH secretion (67–69) which point to an exaggerated secretion of β-endorphin in the disease. Our hypothesis is that low-frequency EA restores opioid tone and improve related symptoms in PCOS (Fig. 2).

Clearly, acupuncture and specifically low-frequency EA affect PCOS symptoms via modulation of endogenous regulatory systems, including the sympathetic nervous system, the endocrine system and the neuroendocrine system (55, 70). The changes are most likely mediated via the endogenous opioid system (55, 70). Figure 2 shows a hypothetical model of the effects of acupuncture in PCOS.

Effects on metabolic pattern

Low-frequency EA with repetitive muscle contractions activate physiological processes similar to those resulting from physical exercise. Daily low-frequency EA treatment induces weight loss and increases insulin sensitivity, reducing blood glucose and lipid levels (71, 72). Repeated low-frequency EA reduces food intake and body weight, possibly by increasing leptin levels in both rats (71) and humans (72–75). Low-frequency EA also stimulates glucose transport in skeletal muscle independently of insulin and increase the insulin sensitivity of glucose transport in rats (76–78). In female rats with PCOS, induced by continuous prepubertal administration of DHT (51), we found that both repeated low-frequency EA treatment and 4–5 weeks of voluntary exercise reduced insulin resistance (unpublished data). Exercise also reduced body fat and body weight and increased lean body mass. Thus, repeated low-frequency EA may reduce insulin resistance, a central feature of PCOS.

Effects on ovulation

The effect of acupuncture on ovulation in PCOS has been evaluated only in case-control studies. In one study, 12 of 24 women with undefined ovulatory dysfunction treated with manual acupuncture (average, 30 treatments) had marked improvements in menstruation and biphasic basal body temperature for more than two cycles or became pregnant (79). Regulatory effects were also shown on LH, follicle-stimulating hormone (FSH) and 17β-oestradiol, indicating an influence on the HPG axis. In another study, 11 anovulatory women (nine with PCOS) received low-frequency EA (three sessions/day, 3 days/cycle) to induce ovulation (80). Ovulation was induced in six of 13 menstrual cycles. EA had no effect in controls. In the anovulatory women, high plasma β-endorphin levels and low hand skin temperature, indicating increased sympathetic nervous activity, were improved by EA, likely reflecting inhibition of the sympathetic nervous system (80). In another study, one single acupuncture treatment along with human menopausal gonadotrophin treatment induced ovulation in infertile women as effectively as human chorionic gonadotrophin treatment (81). However, acupuncture had the advantage of reducing the occurrence of ovarian hyperstimulation syndrome. In infertile women with hormonal disturbances, auricular acupuncture demonstrated pregnancy rates equivalent to those induced by hormonal treatment (82) but with fewer side-effects and miscarriages.

We studied the effect of low-frequency EA treatments on endocrine and neuroendocrinological parameters and anovulation in 24 anovulatory women with PCOS (62). EA increased ovulation in nine women (38%) from this group. The mean monthly rate of ovulation/woman increased from 0.15 before EA to 0.66 during and afterwards (P = 0.004). Three months after the last treatment, the LH/FSH ratio and testosterone concentrations were significantly decreased (62).

These studies demonstrate that low-frequency EA affects endocrine, neuroendocrine and metabolic disturbances in PCOS without any negative side-effects. Indeed, EA can be a suitable alternative or complement to pharmacological induction of ovulation. However, controlled randomised studies are required to verify these results. None of these studies has revealed the mechanisms responsible for the beneficial effects of EA.

Effects on the sympathetic nervous system

Transsection of the superior ovarian nerve in EV-induced PCO rats reduces the steroid response, increases β2-adrenoceptor expression to more normal levels and restores oestrous cyclicity and ovulation (41). Furthermore, blockade of endogenous NGF action restore the EV-induced changes in ovarian morphology and expression of the sympathetic markers α1- and β2-adrenoceptors, p75 neurotrophin receptor p75NTR, NGF-tyrosine kinase receptor and tyrosine hydroxylase. These data confirm that there is a close interaction between NGF and the sympathetic nervous system in the pathogenesis of steroid-induced PCO rats (83).

In line with these observations, repeated low-frequency EA reduces high ovarian concentrations of NGF (45, 46), CRF (61) and endothelin-1 (46) in EV-induced PCO. It also increases low hypothalamic β-endorphin concentrations and immune function (63) in the same rat PCO model. Low-frequency EA stimulates ovarian blood flow, indicating decreased ovarian sympathetic activity (84). To investigate the hypothesis that repeated low-frequency EA treatments and physical exercise modulate sympathetic nerve activity in rats with EV-induced PCO, we studied the expression of mRNA and protein of α1α-, α1β-, α1γ- and β2β-adrenoceptors and the NGF receptor p75NTR and immunohistochemical expression of TH. Four weeks of physical exercise almost normalised ovarian morphology (85), and both EA and exercise normalised the expression of NGF, NGF receptors and α1α- and α1β-adrenoceptors (86). The results indicate that low-frequency EA and physical exercise both modulate sympathetic nervous activity and demonstrate functional interactions between the nervous and endocrine systems, consistent with a therapeutic effect.
Effects on mental health

A recent review examined the efficacy and adverse effects of acupuncture in the treatment of depression (87). There is a lack of well designed randomised controlled trials to evaluate the role of acupuncture in the treatment of depression. However, in a recent study, 33 women with depression were treated with acupuncture for 8 weeks (88). The response rate and relapse rate were similar to those reported with other validated treatments, indicating that acupuncture might be helpful in the treatment of depression (88). This comprises an important field for further exploration with a focus on women with PCOS.

Factors that influence the outcome of acupuncture

Evidence exists that the physiological responses produced by acupuncture vary depending on site, intensity and duration of stimulation (70). Acupuncture intensity can vary enormously depending on the form of stimulation used (e.g. superficial skin needling, sham non-acupuncture point needling, or placebo needling where a blunt tip of a needle touches skin without penetrating) (89, 90). Other acupuncture confounders that may influence outcome are duration of stimulation, number of needles inserted and needle diameter, as well as psychological factors and the environment.

Is acupuncture real or is it a placebo effect?

The control situation in acupuncture studies has widely been discussed and the following biases challenge the concept of acupuncture study designs.

When a needle penetrates the skin, it should be considered as a form of sensory stimulation that activates afferent nerve fibres. Recently, light touch of the skin has been shown to stimulate mechanoreceptors coupled to slow conducting unmyelinated (C) afferents (91) that modulate activity in the central nervous system (91).

In many acupuncture studies, two different acupuncture techniques have been compared (e.g. superficial skin acupuncture needling and deep muscle acupuncture needling). We believe that it is the intensities of acupuncture that are compared; the acupuncture procedure itself is not controlled because the control treatment is not a physiologically inert treatment. It is likely that the control procedures in many acupuncture studies, which are meant to be inert, actually activate C tactile afferents and consequently elicit physiological responses (92). This could explain why superficial, sham acupuncture is as effective as deep muscle acupuncture (93); superficial, sham acupuncture and placebo needling acupuncture cannot be considered as placebo procedures because they are not inert.

Future perspectives

The effect of acupuncture depends on the stimulation and amount of needles, the frequency, duration and amount of acupuncture treatments, as well as environmental and psychological factors. With this in mind, we think that standardisation and fixed study protocols, where all patients receive the same treatment, will increase the validity of acupuncture studies. Fixed study protocols may bias the outcome, but we believe that they are necessary.

More precise standards for reporting randomised controlled trials of acupuncture are needed to overcome difficulties in analysis and interpretation. The revised recommendations for improving the quality of reports of parallel-group randomised trials (CONSORT) statement addresses general difficulties (94). However, certain aspects are insufficiently covered. The Standards for reporting interventions in controlled trials of acupuncture (STRICTA) group have made recommendations to improve reporting of interventions in controlled trials of acupuncture. The STRICTA checklist should be used in conjunction with CONSORT to improve critical appraisal, analysis, and replication of trials (95).

Conclusion

Despite the lack of a large body of evidence, we should not ignore the fact that many women with PCOS use acupuncture. This alone is a compelling reason to investigate the method. In the hands of competent registered health-practitioners, acupuncture is safe (96). Clinical and experimental evidence shows that acupuncture can be a suitable alternative or complement to pharmacological induction of ovulation in women with PCOS and may also relieve other symptoms, without adverse side-effects. Clearly, acupuncture modulates endogenous regulatory systems, including the sympathetic nervous system, the endocrine system and the neuroendocrine system. However, randomised controlled trials are needed to evaluate the effect of acupuncture in women with PCOS.

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References


