Autonomic Neuroscience: Basic and Clinical 157 (2010) 46–51

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

# Effects and mechanisms of acupuncture in the reproductive system

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ARTICLE INFO

*Article history:*
Received 17 December 2009
Accepted 8 March 2010

*Keywords:*
Acupuncture
Reproduction
Steroids
Ovulation
Polycystic ovary syndrome
Sympathetic nerve activity

ABSTRACT

The use of acupuncture to treat reproductive dysfunction has not been well investigated. Only a few clinical studies have been reported, most of which are flawed by poor design and a lack of valid outcome measures and diagnostic criteria, making the results difficult to interpret. Experimental studies, however, show that acupuncture has substantial effects on reproductive function. Here we review the possible mechanisms of action of acupuncture on the reproductive system and its effects on reproductive dysfunction, focusing in particular on polycystic ovary syndrome, the most common endocrine and metabolic disorder in women. Clinical and experimental evidence demonstrates that acupuncture is a suitable alternative or complement to pharmacological induction of ovulation, without adverse side effects. Clearly, acupuncture modulates endogenous regulatory systems, including the sympathetic nervous system, the endocrine system, and the neuroendocrine system. Randomized clinical trials are warranted to further evaluate the clinical effects of acupuncture in reproductive disorders.



## 1. Introduction

Traditional Chinese medicine (TCM) has a long clinical tradition, and gynecology is one of its four major clinical sciences, along with internal medicine, surgery, and pediatrics. Western medicine and TCM differ considerably in their foundations: western medicine is based on scientific and clinical evidence, while TCM evolved from a holistic and macroscopic perspective.

Acupuncture is an integral component of TCM and has become more established in Western medicine over the last decade. Attempts to merge Western and Chinese medicine have not in general been successful. The lack of scientific documentation and poor research methods have led to skepticism over the effects claimed for acupuncture. Moreover, the underlying mechanisms of acupuncture are often described in the language of TCM and are rarely discussed in terms of biological events. Unlike TCM, *Western* acupuncture models rely on physiological and psychological responses to acupuncture. Both views involve stimulating specific anatomic locations on the body by penetrating the skin with thin needles. In TCM, acupuncture points are defined and selected based on knowledge drawn from ancient texts and over 3000–5000 years of clinical experience. In Western acupuncture, acupuncture points are selected according to the innervation of the target organ.

The use of acupuncture to treat reproductive dysfunction has not been well investigated. Only a few clinical studies have been reported, and most are flawed by poor design and a lack of valid outcome measures and diagnostic criteria, making the results difficult to interpret. In this review, we describe possible mechanisms of action, experimental studies, and available clinical data on the use of acupuncture to treat reproductive dysfunction. In particular, we focus on polycystic ovary syndrome (PCOS), the most common endocrine and metabolic disorder in women.

## 2. What is the physiological basis for acupuncture?

Many argue that the effect of acupuncture is implausible because it relies on concepts of changing the flow of energy in meridians. To refute this argument, an understanding of the physiology of acupuncture is important. Intramuscular needle insertion and stimulation cause a particular pattern of afferent activity in peripheral nerve (A-$\delta$ and C) fibers (Kagitani et al., 2005) (Fig. 1). After insertion, acupuncture needles are stimulated by manual manipulation and/or by electrical stimulation, so called electro-acupuncture (EA) for 20–40 min. During EA, needles are attached to electrodes to pass an electrical current. Low-frequency (1–15 Hz) EA with repetitive muscle contraction is thought to activate physiological processes similar to those resulting from physical exercise (Kaufman et al., 1984) that are normally activated during muscle contractions.

Stimulation of acupuncture points in muscle tissue causes local release of neuropeptides—including substance P, calcitonin gene-related peptide, vasointestinal peptide, and neuropeptide Y from the

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doi:10.1016/j.autneu.2010.03.006

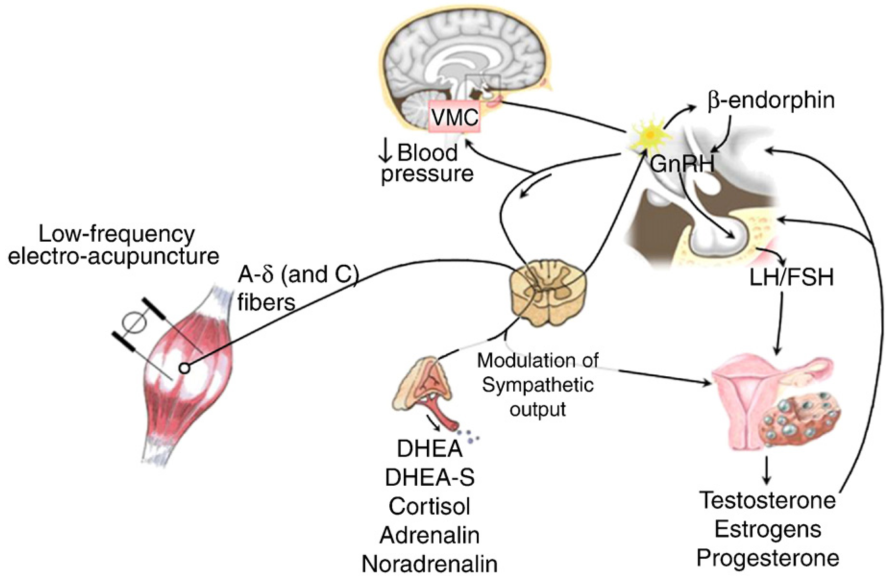


**Fig. 1.** A hypothetical model of the effects of low-frequency EA on hypothalamus–pituitary–ovarian axis and sympathetic nervous system. Needle insertion in to the skin and muscle excite ergoreceptors and cause afferent activity in Aδ-, and C-fibers. Needles placed and stimulated in the same somatic innervation area as the ovary decrease sympathetic nerve activity, which leads to decreased secretion and release of ovarian androgens. In parallel, the activity of higher control systems is modulated either directly or by the release of opioids, in particular β-endorphin, that induce functional changes in different organ systems. In women with PCOS, sympathetic nerve activity and β-endorphin production/release are increased. Low-frequency EA decreases the central β-endorphin release, leading to decreases in sympathetic tone and LH pulse frequency and amplitude, which in turn decrease ovarian androgen production. DHEA, dihydroepiandrosterone; DHEA-S, sulfate ester of DHEA.

peripheral nerve terminals (Dawidson et al., 1997; Jansen et al., 1989; Sato et al., 2000)—into the surrounding area. As a result, microcirculation and glucose uptake are increased, the latter most likely through a reflex response from muscle twitches during manual or electrical stimulation (Higashimura et al., 2009).

Depending on the number and location of needles and the intensity and type of stimulation (White et al., 2008), activation of muscle afferents also modulates the transmission of signals in the spinal cord (segmental level) and in the central nervous system (CNS). At the segmental (spinal) level, acupuncture may modulate, through sympathetic reflexes, organs such as the ovaries that are located in the same innervation area as the stimulated acupuncture points (Sato et al., 1997; Stener-Victorin et al., 2003a). Simultaneously, the nervous system transfers signals to the brain, which yields a response that may also affect the organ. Both segmental and central mechanisms of acupuncture are most likely involved in the total effect of acupuncture treatment (Stener-Victorin et al., 2006). Since the CNS regulates the release of hormones from pituitary, acupuncture may also modulate the endocrine system (Stener-Victorin et al., 2008).

Specifically, low-frequency EA causes release of many neuropeptides, serotonin, endogenous opioids, and oxytocin in the CNS, which seem to be essential for inducing functional changes in different organ systems (Andersson and Lundeberg, 1995; Stener-Victorin et al., 2008). Of particular interest is β-endorphin, an endogenous opioid with high affinity for the μ-opioid receptor (Basbaum and Fields, 1984). The central hypothalamic β-endorphin system has a regulatory role in a variety of functions, including reproduction and autonomic function (Andersson and Lundeberg, 1995; Eyvazzadeh et al., 2009). β-endorphin is produced and released from hypothalamic nucleus arcuatus and the nucleus tractus solitarius in the brain stem, which project to a number of sites within the brain, including all parts of the hypothalamus (Ferin et al., 1984).

β-endorphin is a key mediator of changes in autonomic functions. Through effects on the vasomotor centre, for example, it can result in a general decrease of sympathetic tone, shown as a reduction in blood pressure and decreased muscle sympathetic nerve activity (Andersson and Lundeberg, 1995; Yao et al., 1982). Hypothalamic β-endorphin also interacts with the hypothalamic–pituitary–ovarian axis by exerting a tonic inhibitory effect on the gonadotropin releasing hormone (GnRH) pulse generator and on pituitary luteinizing (LH) release (Genazzani et al., 1993; Jenkins and Grossman, 1993). β-endorphin is also released into peripheral blood from the hypothalamus via the anterior pituitary (Crine et al., 1978), a process regulated by corticotropin-releasing factor (CRF), which is secreted from the paraventricular nucleus of the hypothalamus (Chan et al., 1982). CRF promotes the release of β-endorphin, adrenocorticotropic hormone, and melanocyte-stimulating hormone into the blood stream in equimolar amounts by stimulating the synthesis of their precursor, pro-opiomelanocortin. β-endorphin in plasma is thought to be related to the hyperinsulinemic response (Carmina et al., 1992) and stress (Lobo et al., 1983). Stress increases the activity of the hypothalamic-pituitary-adrenal (HPA) axis and decreases reproductive functions. Thus, hormones of the HPA axis are closely related to those of the hypothalamic-pituitary-ovarian axis. CRF, adrenocorticotropic hormone, β-endorphin, and adrenal corticosteroids all modulate the effects of stress on reproductive functions (Rivier and Rivest, 1991).

Acupuncture may hypothetically affect the HPA axis by decreasing cortisol concentrations (Harbach et al., 2007) and the hypothalamic–pituitary–gonadal (HPG) axis by modulating central β-endorphin production and secretion, thereby influencing the release of hypothalamic GnRH and pituitary secretion of gonadotropin (Stener-Victorin et al., 2008). It may also decrease hyperinsulinemia by lowering high concentrations of circulating β-endorphin (Stener-Victorin et al., 2000b). The central and peripheral β-endorphin systems operate independently, but both can be stimulated by afferent nerve activity induced by manual acupuncture and EA (Andersson and Lundeberg, 1995).

## 3. How does acupuncture work in women with PCOS and reproductive dysfunction?

The primary etiology of PCOS is incompletely understood and remains a hen-and-egg mystery, despite the high prevalence of the syndrome. Ovarian hyperandrogenemia, the most consistent endocrine feature of PCOS, probably plays a key role in its etiology (Abbott et al., 2002; Gilling-Smith et al., 1997). Hyperinsulinemia and insulin resistance as well as abdominal obesity are also thought to be important etiological factors in PCOS (Barber et al., 2006; Dunaif and Thomas, 2001). Neuroendocrine defects appear to be important, too, as persistently rapid LH pulsatility and increased amplitude further augment ovarian androgen production (Blank et al., 2007). β-endorphin is an inhibitory modulator of the GnRH pulse generator and pituitary LH release, and thus PCOS may partly result from insufficient central β-endorphin inhibition of GnRH. Evidence that β-endorphin contributes to the pathogenesis of PCOS and dysregulation of GnRH/LH secretion comes from studies showing that the μ-receptor antagonists naltrexone or naloxone improve menstrual cyclicity, induced ovulation, and decrease insulin and LH levels, the LH/follicle stimulating hormone (FS) ratio, and testosterone levels (Ahmed et al., 2008; Ciampelli et al., 1998; Fruzzetti et al., 2002; Fulghesu et al., 1998; Hadziomerovic et al., 2006; Lanzone et al., 1995). Because the effects of acupuncture may be mediated at least in part by modulation of β-endorphin production and secretion, which in turn affect GnRH/LH secretion, we hypothesize that acupuncture reduces ovulatory dysfunction and thus decreases the secretion of ovarian androgens in women with PCOS.

Circulating β-endorphin levels are increased in women with PCOS (Wortsman et al., 1984). This finding suggests that a dysregulated peripheral opioid system may play a role in the pathophysiology of insulin resistance and compensatory hyperinsulinemia in PCOS. Opioids can stimulate insulin production (Bruni et al., 1979) and inhibit its clearance by the liver (Fulghesu et al., 1998), thereby contributing to the hyperinsulinemia often observed in PCOS. Several studies have shown that inhibition of opioid tone with naltrexone or naloxone reduces hyperinsulinemia in women with PCOS (Fruzzetti et al., 2002; Fulghesu et al., 1998; Hadziomerovic et al., 2006), likely by speeding insulin clearance or increasing the insulin sensitivity of target tissues (Fulghesu et al., 1998; Hadziomerovic et al., 2006). Interestingly, low-frequency EA decreases high circulating concentrations of β-endorphin in women with PCOS and may hypothetically decrease hyperinsulinemia and increase insulin clearance or sensitivity (Chen and Yu, 1991; Stener-Victorin et al., 2000b).

Many factors associated with PCOS—including disturbed central and peripheral β-endorphin release, hyperandrogenemia, hyperinsulinemia and insulin resistance, abdominal obesity, and cardiovascular disease—are also associated with increased sympathetic nervous system activity (Dissen et al., 2009a; Fagius, 2003; Ojeda and Lara, 1989; Reaven et al., 1996; Sir-Petermann et al., 2002). The involvement of the sympathetic nervous system in PCOS pathology is further supported by the abnormally high density of catecholaminergic nerve fibers in polycystic ovaries (PCO) (Heider et al., 2001; Semenova, 1969). Increased ovarian sympathetic nerve activity might contribute to PCOS by stimulating androgen secretion (Greiner et al., 2005). Recently it was demonstrated that women with PCOS have enhanced ovarian productions of nerve growth factor (NGF) (Dissen et al., 2009b), a strong marker of sympathetic nerve activity. These results suggest that overproduction of ovarian NGF is a component of PCO morphology in humans. In a transgenic mouse model overexpressing NGF in the ovaries, persistent elevation in plasma LH levels is required for the morphological abnormalities to appear (Dissen et al., 2009b). These results may explain why ovarian wedge resection or laparoscopic laser cauterization (Balen, 2006), which likely temporary disrupt ovarian sympathetic innervation, increase ovulatory function and decrease androgen synthesis in women with PCOS.

In our recent study, direct intraneural recording demonstrated that women with PCOS have high sympathetic nervous system activity that may be relevant to the pathophysiology of the syndrome (Sverrisdottir et al., 2008). Interestingly, testosterone was the strongest independent factor linked to the high sympathetic activity. Since the androgen concentration can reflect the severity of PCOS, the relationship between muscle sympathetic nerve activity and testosterone concentration indicates that the degree of sympatho-excitation is related to the degree of PCOS severity. The augmented sympathetic activity may contribute to the vascular risk factors associated with the syndrome. Thus, therapies aimed at reducing sympathetic activity in women with PCOS need to be studied.

Fig. 1 illustrates how acupuncture—and specifically low-frequency EA—may improve reproductive dysfunction and PCOS-related symptoms by modulating endogenous regulatory systems, including the sympathetic nervous system, endocrine system, and the neuroendocrine system (Andersson and Lundeberg, 1995; Stener-Victorin et al., 2008).

In the treatment of reproductive dysfunction according to Western medical acupuncture, acupuncture needles are placed in the abdominal muscles and in the muscles below the knee in somatic segments corresponding to the innervation of the ovaries (Th12-L2, S2-S4) (Bonica, 1990). To strengthen and prolong the effect on the CNS, additional points extrasegmental to the ovaries are selected bilaterally in the muscles of the arm below the elbow (Thomas and Lundberg, 1994; Thomas and Lundeberg, 1996). Classical acupuncture points are not the only places where the nervous system can be stimulated. But they are often used in research because their anatomical location and innervations are well described. Thus, classical acupuncture points are not specific, and needle insertion at other sites in the same segmental innervation most likely cause similar effects.

## 4. What evidence exists for use of acupuncture in PCOS and reproductive dysfunction?

### *4.1. Effects on ovulation*

The effects of acupuncture on ovulatory dysfunction in PCOS have been evaluated only in case–control studies. In one study, 11 anovulatory women (9 with PCOS) received low-frequency EA (3 days/cycle, 13 cycles) to induce ovulation (Chen and Yu, 1991). Ovulation was induced in 6 of 13 menstrual cycles. Anovulatory women displayed high plasma β-endorphin levels and low hand skin temperature, indicating increased sympathetic nervous activity, which was improved by EA, likely reflecting inhibition of the sympathetic nervous system (Chen and Yu, 1991).

In a nonrandomized trial, auricular acupuncture, once a week for 3 months, was compared to hormone treatment in infertile women with hormonal disturbances ($n=45$ per group) (Gerhard and Postneek, 1992). Acupuncture yielded pregnancy rates equivalent to those induced by hormonal treatment but with fewer side effects and miscarriages. In another study, 12 of 24 women with undefined ovulatory dysfunction treated with manual acupuncture (average, 30 treatments) (Xiaoming et al., 1993) displayed marked improvements in menstruation and biphasic basal body temperature for more than two cycles or became pregnant. Regulatory effects on LH, FSH, and estradiol were shown, indicating an influence on the HPG axis.

In an uncontrolled trial, we evaluated the effect of low-frequency EA treatments (14 treatments) on endocrinological and neuroendocrinological parameters and ovulation in 24 anovulatory women with PCOS (Stener-Victorin et al., 2000b). In nine (38%), EA increased ovulation. The mean monthly rate of ovulation/woman increased from 0.15 before EA to 0.66 during and afterward ($p=0.004$). Three months after the last treatment, the LH/FSH ratio and testosterone concentrations were significantly decreased.

To prevent exacerbation of ovarian hyperstimulation syndrome, acupuncture was given in place of human chorionic gonadotropin (hCG) after treatment of infertile women with human menopausal gonadotropin (hMG). A single acupuncture treatment induced ovulation as effectively as the combination of hMG and hCG (Cai, 1997) and reduced the occurrence of ovarian hyperstimulation syndrome. These results are consistent with those of an experimental study in which acupuncture given on day 1, 2 and 3 after injection with pregnant mare serum gonadotropin and hCG improved the ovarian response and increased egg production in female mice (Jin et al., 2009). The positive effect of acupuncture may be associated with regulation of ovarian expression of FSH receptor mRNA.

Other experimental studies support the beneficial clinical effects of acupuncture on the HPG axis. Female rats continuously exposed to 5α-dihydrostestosterone (DHT) from puberty display reproductive and metabolic features of PCOS (Mannerås et al., 2007). Rats with DHT-induced PCOS have disrupted estrous cyclicity and PCO-like ovarian morphology. Repeated low-frequency EA (3 days/week for 4–5 weeks) and physical exercise improved ovarian morphology, as reflected in a higher proportion of healthy antral follicles and a thinner theca interna cell layer than in untreated PCOS rats (Manneras et al., 2009). More intensive low-frequency EA (5 days/week for 4–5 weeks) normalized estrous cyclicity to an even greater extent (Feng et al., 2009). Repeated low-frequency EA also increases aromatization in adipose and liver tissue and promotes circulating estrogen concentrations in ovariectomized (OVX) rats (Zhao et al., 2004).

### 4.2. Effects on the CNS

Exposure of female rats to DHT increases both the number of hypothalamic cells expressing GnRH and the expression androgen receptor (AR) protein in the hypothalamus. Intensive low-frequency EA given 5 days/week for 4–5 weeks restored normal levels of GnRH and AR expression in rats with DHT-induced PCOS (Feng et al., 2009). The distribution of AR and GnRH overlapped, indicating a potential mechanism for the regulation of GnRH-expressing neurons by androgens. This possibility was further confirmed by the co-localization of AR and GnRH in the MPO, including both cytoplasmic and nuclear expression.

Repeated low-frequency EA also modulates CRF levels in the median eminence in rats with estradiol valerate (EV)-induced PCO and in the hypothalamus in OVX rats (Stener-Victorin et al., 2001; Zhao et al., 2003a). In OVX rats, it also increase serum estradiol levels and hypothalamic GnRH expression (Zhao et al., 2003a; Zhao et al., 2003b) and the number of GnRH neurons (Zhao et al., 2005). In addition, repeated low-frequency EA modulates hypothalamic GnRH mRNA expression during sexual development, further supporting the notion that acupuncture modulates the HPG axis (Zhaohui et al., 2007).

These results may help explain the beneficial neuroendocrine effects of low-frequency EA in women with PCOS. They also indicate that more intensive treatment results in more pronounced effects.

### 4.3. Effects on the sympathetic nervous system

Recently, we demonstrated that low-frequency EA *and* physical exercise lower high sympathetic nerve activity in women with PCOS. This novel finding shows that treatment with low-frequency EA or physical exercise with the aim of reducing muscle sympathetic nerve activity may be of importance for women with PCOS (Stener-Victorin et al., 2009).

In the EV-induced rat PCO model, transection of the superior ovarian nerve reduces the steroid response, increases $\beta_2$-adrenoceptor expression to more normal levels, and restores estrus cyclicity and ovulation (Barria et al., 1993). Also, blockade of endogenous NGF action restores the EV-induced changes in ovarian morphology and expression of the sympathetic markers $\alpha_1$- and $\beta_2$-adrenoceptors, p75 neurotrophin receptor p75$^{NTR}$, NGF-tyrosine kinase receptor, and tyrosine hydroxylase. These data confirm the close interaction between NGF and the sympathetic nervous system in the pathogenesis of steroid-induced PCO in rats (Manni et al., 2005b). In line with these observations, repeated low-frequency EA in rats with EV-induced PCO lowers the high ovarian concentrations of NGF (Stener-Victorin et al., 2003b; Stener-Victorin et al., 2000a), CRF (Stener-Victorin et al., 2001), and endothelin-1 (Stener-Victorin et al., 2003b). This treatment also modulates hypothalamic β-endorphin concentrations and immune function (Stener-Victorin and Lindholm, 2004) in this model.

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 mRNA and protein expression of $\alpha_{1a}$-, $\alpha_{1b}$-, $\alpha_{1d}$-, and $\beta_2$-adrenoceptors and the NGF receptor p75$^{NTR}$ and immunohistochemical expression of tyrosinhydroxylase. Four weeks of physical exercise almost normalized ovarian morphology (Manni et al., 2005a), and both EA and exercise led to normal expression of NGF, NGF receptors, and $\alpha_1$- and $\alpha_2$-adrenoceptors (Manni et al., 2005a; Manni et al., 2005b). In mesenteric adipose tissue, mRNA expression of beta-3 adrenergic receptor, NGF, and neuropeptide Y was higher in untreated rats with DHT-induced PCOS than in controls. Low-frequency EA and exercise downregulated mRNA expression of NGF and neuropeptide Y, and EA also downregulated expression of the beta-3 adrenergic receptor, compared with untreated rats with DHT-induced PCOS. Interestingly, EA did not affect fat mass.

In another study, we found that low-frequency, but not high frequency (80–100 Hz), EA increases ovarian blood flow. The needles were placed in the abdominal and hind limb muscles, which have the same somatic innervation as the ovaries and uterus (Stener-Victorin et al., 2006; Stener-Victorin et al., 2003a; Stener-Victorin et al., 2004). The response was mediated by ovarian sympathetic nerves as a reflex response, and the reflexes were controlled by supraspinal pathways (i.e., CNS) (Stener-Victorin et al., 2006; Stener-Victorin et al., 2003a).

These findings support the theory that increased sympathetic activity contributes to the development and maintenance of PCOS and that the effects of EA, and also exercise, may be mediated by modulation of sympathetic outflow to the adipose tissue and ovaries.

## 5. Future perspectives

The effects of acupuncture depend on the type of stimulation (manual and/or electrical), the stimulation frequency (number of manual manipulations and/or frequency of electrical stimulation), the number of acupuncture needles inserted, how often treatment is applied, and the number and duration of acupuncture treatments, as well as environmental and psychological factors. Thus a large number of variables may affect the outcome of an acupuncture study. With this in mind, standardization and *fixed study protocols,* in which 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. Further, it is time to perform randomized clinical trials to compare acupuncture to the best available treatment rather than to a sham needling, which is not inert.

More precise standards for reporting randomized clinical trials of acupuncture are needed to overcome difficulties in analysis and interpretation. 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 (Prady et al., 2008).

## 6. Conclusion

Despite the lack of a large body of evidence, we should not ignore the fact that many women with reproductive disorders, and in particular women with PCOS, use acupuncture. Clinical and experimental evidence demonstrates that acupuncture can be a suitable alternative or complement to pharmacological induction of ovulation, without adverse side effects. Clearly, acupuncture modulates endogenous regulatory systems, including the sympathetic nervous system, the endocrine system, and the neuroendocrine system. Randomized clinical trials are warranted to evaluate the clinical effect of acupuncture in reproductive disorders.

## Acknowledgments

There is no conflict of interest that would prejudice the impartiality of this scientific work. This study was financed by grants from the Swedish Medical Research Council (Project No. 2008-72VP-15445-01A), Novo Nordisk Foundation, Wilhelm and Martina Lundgrens's Science Fund, Hjalmar Svensson Foundation, Tore Nilson Foundation, Åke Wiberg Foundation, Adlerbert Research Foundation, Ekhaga Foundation, and the Swedish federal government under letters of understanding agreement of Medical Education (ALFFGBG-10984) and Regional Research and Development agreement (VGFOUREG-5171, -11296, and -7861).

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