Acupuncture for insulin sensitivity in women with polycystic ovary syndrome

Dear Sir,

We would like to thank Dr Palomba (2022) for the interest in our work. We appreciate the opportunity to respond.

Our study aimed to reveal whether acupuncture with needles inserted into acupuncture points in skeletal muscle and stimulated with low-frequency electrical stimulation improves insulin sensitivity more effectively than metformin or sham acupuncture with superficial needle insertion in women with polycystic ovary syndrome (PCOS) and insulin resistance (IR). The total dropout rate was 17.8% after a 4-month treatment and 23.4% at the 3-month follow-up; although high it is comparable with other clinical trials. We do agree that per-protocol (PP) analysis might give a more correct direction of the metabolic effect of acupuncture and therefore performed both intention-to-treat (ITT) and PP analyses with similar results (Table I). Acupuncture is a pragmatic treatment in the clinic and ITT analysis reflects the reality that nonadherence occurs in real-world practice; therefore, ITT analysis is best used when investigating efficacy and safety.

The most effective and optimal mode of acupuncture treatment for the improvement of insulin sensitivity is unknown. What we do know is that two previous uncontrolled clinical trials using exactly the same 'true' acupuncture protocol as in the present study demonstrated an improvement in insulin sensitivity after 5 weeks and after 3 and 6 months of treatment, respectively (Zheng *et al.*, 2015; Stener-Victorin *et al.*, 2016; Li *et al.*, 2020). There are a large number of variables, such as type of stimulation (manual vs electrical, high vs low frequency, high vs low intenstity), which acupuncture points are used, depth of needle insertion, number of acupuncture points selected, thickness of the acupuncture needles and so on. What is most important is to clearly describe exactly how acupuncture was performed to enable repetition. There are no previous studies comparing different acupuncture protocols in the treatment of metabolic disorders in women with PCOS. Therefore, based on our previous studies, a standardized acupuncture protocol was used in the present study. Personalized acupuncture has been used in some diseases and its effectiveness has been confirmed (Macklin *et al.*, 2006; Cherkin *et al.*, 2009; Ko *et al.*, 2016; Garland *et al.*, 2019). We are currently conducting a multicenter randomized controlled trial (RCT) in infertile women with PCOS to explore the effect of a standardized acupuncture versus personalized acupuncture on live birth rate; the study protocol has been published (ClinicalTrials.gov, NCT03625531) (Huang *et al.*, 2020).

Establishing an inert sham electroacupuncture control remains methodologically challenging especially because acupuncture relies on activation of sensory afferents and as soon as something touches the skin there is an activation. Based on the results in the present study, the sham procedure was likely not inert as we observed an improvement also in the sham acupuncture treatment arm. Chen *et al.* (2017) systematically investigated sham electroacupuncture methods from 94 RCTs. Sham electroacupuncture at non-acupuncture points with superficial insertion and no electrical stimulation is one of the most commonly used sham electroacupuncture and validation of credibility i.e. whether included participants know which group they were assigned was reported in most studies. The sham acupuncture protocol used in our study was consistent with the method used in an RCT published in *JAMA* (Wu *et al.*, 2017). With that said, whether the sham procedure used in our present study really can be considered as 'sham' is a good question. Per definition—no. We do agree that there is no optimal sham procedure and all types of 'sham' acupuncture procedures introduce study bias. However, as researchers, we are obliged to use sham protocols in our studies. In the present study, needles in the 'sham' acupuncture group were inserted superficially in non-acupuncture positions on the shoulder and upper arm bilaterally with a depth of <5 mm and connected to an electrical stimulator with mimetic electricity and no manual stimulation (Li *et al.*, 2017; Wen *et al.*, 2022). Placement of needles is unlikely to affect ovulation and IR in women with PCOS. Furthermore, we analyzed the subjects who had previous acupuncture experience at baseline. The results showed that there was no significant difference between the true and sham acupuncture treatments. Additionally, skilled acupuncturists with at least 5 years of experience in acupuncture were specially trained for the trial. Therefore, we consider that there was no concern about true and sham acupuncture in this study.

We agree with Dr Palomba that age may affect the outcome in women with PCOS, but metabolic features are not improved by age. Importantly, there was no difference in subjects' age between the groups with median (interquartile range) in true acupuncture, metformin and sham group: 27.0 (25.0 to 31.0), 27.0 (25.0 to 30.0) and 27.0 (24.0 to 29.0), respectively.

Lifestyle modification is the primary treatment for women with PCOS (Palomba *et al.*, 2008, 2010) and diet and physical exercise changes could influence the metabolic results. Therefore, during the treatment and follow-up period of the study, all subjects were informed to have regular physical exercise and healthy diet at the baseline visit to ensure the comparability of the three treatments. We recorded the International Physical Activity Questionnaire at baseline, after 4 months of treatment and after 3 months of follow-up to evaluate physical activity during the study. The result showed that there was no significant difference in the degree of physical activity between groups at any time point and it is therefore unlikely that this would have had an impact on the outcome (Wen *et al.*, 2022).

PCOS is a heterogeneous disorder, not only in terms of pathophysiology but also in the severity of its clinical consequences. There are differences between the phenotypes of PCOS, and the response to treatments may vary according to different phenotypes. As suggested, it would be of interest to define the impact of the four phenotypes on the effect of treatment. However, between the groups in true acupuncture, metformin and sham group in our study at baseline: 32 (28.1%), 33 (28.9%), 32 (28.1%) women with hyperandrogenism + ovulatory dysfunction+ polycystic ovarian morphology, 2 (1.8%), 1 (0.9%), 0 (0.0%) women with hyperandrogenism + ovulatory dysfunction, and 80 (70.2%), 80 (70.2%) and 82 (71.9%) women with polycystic ovarian morphology + ovulatory dysfunction, respectively, and there is no woman with hyperandrogenism + polycystic ovarian morphology (Wen *et al.*, 2022). Moreover, menstrual cycle diaries were not assessed in all subjects. Some of the participants received progestin for withdrawal bleeding if they did not menstruate after 2 months, since the focus of this study is not on reproductive indicators.

Table I Changes in HOMA-IR are determined by intention-to-treat (ITT) and per-protocol (PP) analyses.

Parameter	True acupuncture + placebo (true acupuncture)	Sham acupuncture + metformin (metformin)	Sham acupuncture + placebo (sham acupuncture)	Absolute difference between groups (95% CI, *P*-value*)	
				True acupuncture vs sham acupuncture	True acupuncture vs metformin
ITT analysis					
HOMA-IR at 4 months after baseline visit, median (95% CI)	3.3 (3.2 to 4.3)	3.2 (3.4 to 4.4)	3.4 (3.7 to 4.8)		
HOMA-IR at 7 months after baseline visit, median (95% CI)	3.1 (3.0 to 5.2)	3.3 (3.5 to 4.8)	3.6 (3.4 to 4.4)		
Change from baseline to 4 months after baseline visit, median (95% CI)	−0.5 (−0.6 to 0.1)	−1.0 (−1.3 to −0.5)	−0.3 (−0.5 to 0.3)	−0.2 (−0.7 to 0.3)	0.6 (0.1 to 1.1)
No. of subjects	97	96	98	0.38	**0.03**
Changes from baseline to 7 months after baseline visit, median (95% CI)	−0.5 (−0.9 to 1.0)	−0.6 (−0.8 to 0.1)	−0.3 (−0.9 to 0.0)	0.5 (−0.6 to 1.6)	0.4 (−0.7 to 1.5)
No. of subjects	94	82	86	0.89	0.96
PP analysis					
HOMA-IR at 4 months after baseline visit, median (95% CI)	3.4 (3.2 to 4.3)	3.0 (3.2 to 4.1)	3.3 (3.7 to 4.8)		
HOMA-IR at 7 months after baseline visit, median (95% CI)	3.1 (3.0 to 5.2)	3.3 (3.5 to 4.8)	3.6 (3.4 to 4.4)		
Change from baseline to 4 months after baseline visit, median (95% CI)	−0.5 (−0.6 to 0.1)	−1.0 (−1.2 to −0.5)	−0.2 (−0.5 to 0.3)	−0.2 (−0.8 to 0.5)	0.6 (−0.1 to 1.3)
No. of subjects	94	82	86	0.40	**0.04**
Changes from baseline to 7 months after baseline visit, median (95% CI)	−0.5 (−0.9 to 1.0)	−0.6 (−0.8 to 0.1)	−0.3 (−0.9 to 0.0)	0.5 (−0.7 to 1.7)	0.4 (−0.8 to 1.6)
No. of subjects	94	82	86	0.89	0.96

*Between-group comparisons were carried out by Mann–Whitney *U* test. All tests were two-sided, and a *P*-value <0.05 was considered significant.
HOMO-IR, homeostasis model assessment of insulin resistance score.
Bold indicates statistical significance.

Therefore, the current study is not powered to perform the sub-analyses on the changes of phenotypes between groups.

Conflict of interest

None.

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Hongxia Ma[1,2,*], Min Hu[1,2], Qidan Wen[1] and Elisabet Stener-Victorin[1,3,*]

[1]*Department of Traditional Chinese Medicine, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China*
[2]*Institute of Integration of Traditional Chinese Medicine and Western Medicine, Guangzhou Medical University, Guangzhou, Guangdong, China*
[3]*Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden*

*Correspondence address. Department of Traditional Chinese Medicine, The First Affiliated Hospital of Guangzhou Medical University, No. 151 Yan Jiang Road, Yue Xiu District, Guangzhou 510000, China. E-mail: doctorhongxia@126.com (H.M.)
https://orcid.org/0000-0002-4477-613X;
Department of Physiology and Pharmacology, Karolinska Institutet, 17177 Stockholm, Sweden. E-mail: elisabet.stener-victorin@ki.se (E.S.-V.)
https://orcid.org/0000-0002-3424-1502

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