Large randomized controlled trials in reproductive medicine: another battle won by biases and confounders?

Dear Sir,

I read with great interest a randomized controlled trial (RCT) recently published in *Human Reproduction* (Wen *et al.*, 2021). The study is a well-designed trial with a published protocol (Li *et al.*, 2017) and aimed to evaluate the effect of acupuncture on insulin sensitivity, assessed as HOMA-IR score (homeostasis model assessment of insulin resistance score), in comparison to metformin or sham acupuncture, in a large population of women with polycystic ovary syndrome (PCOS). Insulin resistance was defined as a HOMA-IR index equal or higher than 2.14. No difference was observed between acupuncture and metformin in insulin resistance improvement. However, metformin induced a body weight loss higher than acupuncture did; acupuncture reduced significantly the fasting glucose levels in comparison with metformin albeit this reduction was small enough to be considered significant only from a statistical point of view.

It is well known that RCTs are the best way to obtain scientific data with a low risk of bias, and that data analysis using the intention-to-treat analysis is needed to sustain the efficacy of the randomization. However, in the trial by Wen *et al.* (2021), the drop-out rates were very high, reaching about one-third of the patients in two arms; during study design, no implementation of the sample size was defined to replace subjects that dropped out. Thus, per-protocol analysis might give a more correct direction of the metabolic effect of acupuncture.

I was very interested in the acupuncture procedure used in the experimental arm. It is true that this technique has been widely used in other studies, but are there data supporting this technique as the best acupuncture approach (when compared with other points and stimulation locations) for treating metabolic disorders in PCOS (in order to be considered the intervention arm of such a large trial)? Another concern regards the procedure for the sham acupuncture treatment. The authors detail that needles were inserted superficially in non-acupuncture positions on the shoulder and upper arm bilaterally with a depth <5 mm with mimetic electricity and no manual stimulation. May this procedure be really considered as 'sham'? Is it possible that it introduces another study bias?

Women aged 18–40 years were included in the study. Several data have demonstrated that in aged populations with PCOS the syndrome may spontaneously improve such that an asymmetric proportion of patients in a specific age group in different trial arms may influence and confound results. The influence of patients' age on the results would be interesting.

The use of questionnaires or daily diaries would be useful to assess diet during the study period. Patients with PCOS and insulin resistance should be first counselled about lifestyle modification changes (essentially, including a hypocaloric diet plus physical exercise) as the primary treatment for their condition (Palomba *et al.*, 2008, 2010). It should be considered ethically correct to avoid enrolling patients who are compliant with lifestyle modification changes in an experimental study protocol; this is more and more important because obese patients were not excluded from the trial. On the other hand, the inclusion and randomization of women with PCOS under standardized diet and/or physical activity programme could be ethically correct, even if this could introduce a further bias (Palomba *et al.*, 2008, 2010). The latter study design would be closer to clinical practice in order to provide reality-based data.

Finally, considering the large difference in PCOS phenotypes (Orio and Palomba, 2014) it would be very interesting to know the influence, if any, of the four phenotypes on (i) the effectiveness of acupuncture in comparison with metformin administration and sham acupuncture and (ii) menstrual cycle diaries (Li *et al.*, 2017) for anovulatory and ovulatory women with PCOS. Such data could identify potential beneficial or adverse effects, respectively, on menstrual cyclicity.

Conflict of interest

The author has conflict of interest to declare. In particular, he has no commercial or financial interest and/or any other relationships with pharmaceutical manufacturers.

References

Li J, Ng EH, Stener-Victorin E, Hu Z, Shao X, Wang H, Li M, Lai M, Xie C, Su N *et al.* Acupuncture treatment for insulin sensitivity of women with polycystic ovary syndrome and insulin resistance: a study protocol for a randomized controlled trial. *Trials* 2017;**18**:115.

Orio F, Palomba S. Reproductive endocrinology: new guidelines for the diagnosis and treatment of PCOS. *Nat Rev Endocrinol* 2014;**10**:130–132.

Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A, Zullo F, Orio F. Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. *Hum Reprod* 2010;**25**:2783–2791.

Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, Colao A, Vigorito C, Zullo F, Orio F *et al.* Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Hum Reprod* 2008;**23**:642–650.

Wen Q, Hu M, Lai M, Li J, Hu Z, Quan K, Liu J, Liu H, Meng Y *et al.* Effect of acupuncture and metformin on insulin sensitivity in women with polycystic ovary syndrome and insulin resistance: a three-armed randomized controlled trial. *Hum Reprod* 2022;**37**:542–552.

Stefano Palomba*

Department of Gynecology & Obstetrics, University "Magna Graecia" of Catanzaro, Catanzaro, Italy

*Correspondence address. Department of Gynecology & Obstetrics, University "Magna Graecia" of Catanzaro, Catanzaro, Italy.
E-mail: stefanopalomba@tin.it
https://orcid.org/0000-0003-2767-8295

https://doi.org/10.1093/humrep/deac055
Advance Access Publication on March 25, 2022