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Limitations of randomization for the study of nutrition, lifestyle, and in vitro fertilization success



In this issue, Oostingh and colleagues (1) report the results of a multicenter single-blinded, randomized trial performed in the Netherlands that showed modest improvements in nutritional and lifestyle behaviors in couples undergoing in vitro fertilization (IVF) after an mHealth intervention. The participants answered online questionnaires about their behaviors, resulting in access to a personalized page and text messages with tips and feedback on their inadequate behaviors. The control group only answered the online questionnaires. The intervention arm that received the personalized coaching and messages had a 0.8 point lower dietary risk score (out of 9 for women and 6 for men) and a 0.1 point lower lifestyle risk score (out of 9) among the subset of participants with inadequate scores at baseline. Importantly, the participants in the intervention arm were statistically significantly less likely to complete the trial.

We commend the authors for their multisite randomized controlled trial and strategies to minimize selection bias and confounding. In such a study it is inherently impossible for the participants to be blinded to the received treatment. In our own reanalysis of a meta-analysis of the use of acupuncture by similar subfertile women undergoing IVF with intracytoplasmic sperm injection (ICSI), we did confirm a statistically significant improvement in outcomes when the treatment allocation was not blinded, whereas there were no, or even detrimental effects, observed in studies employing a mock acupuncture control (2). We concluded that most likely a placebo effect was occurring because of the medical attention the participants received. This caution regarding single-blinded trials to examine IVF success should not detract from the reasonable assumption that the mHealth online coaching targeted to each patient's specific nutritional and lifestyle deficiencies is a fully logical approach to improving those behaviors.

There are two considerations to raise on the analytic approach. The first is that in intention-to-treat analysis all randomized participants are counted; however, here the comparisons of the change in scores included only the subsets (86% in dietary and 52% in lifestyle analysis) that showed inadequate behaviors at baseline. It is then possible that the true effect size is smaller. Second, the clinical relevance of the outcome is unclear, and the study was not powered sufficiently to examine pregnancy outcomes, nor was there a signal that the intervention group did better, with lower odds for pregnancy (odds ratio 0.87).

Generalizability is always a consideration; for example, in the presence of obesity in a large proportion of subjects, other approaches might be required. All the participants in this study were from the Netherlands. Their mean BMI of 23.8 and mean age of 33 were lower than may be present in some other countries, particularly the United States.

In our University of California San Diego/Reproductive Partners IVF program we have assumed that the physicians and IVF coordinators will have the greatest impact via in-person emphasis on improving these behaviors. At the same time, the information to impart is extensive. Therefore, we have provided it on our IVF program website. Other IVF programs have our permission to copy any of the materials we have placed there. As with the study by Oostingh et al. (1), a blinded study of our approach would not be possible, and we could not consider assigning couples to a control group without access to the materials. However, it would be possible for any program recommending such materials to their patients to assess improvements in those behaviors through questionnaires.

In the Oostingh study, not all behaviors that have been reported to impact IVF success were included, and the percentage of smokers was too low to have enough participants in that category to provide sufficient statistical power. The Mediterranean diet has been reported to improve fertility in both men and women and a part of that diet is fish intake, providing omega-3 fatty acids (3). Exercise also has been reported to improve fertility in both partners (4), and its impact may be the greatest in obese women (5). Environmental factors such as exposures to bisphenol A (BPA) are also covered on our website. Efforts to reduce stress may be the most important of all behaviors positively impacting IVF success, which we have emphasized. Efforts to promote change of the full range of behaviors impacting IVF success would be much more likely to result in a substantial clinical benefit.

The improvements in nutritional and lifestyle behaviors in this study were modest. Having a <1-point improvement in scores emphasizes how very difficult it is for patients to improve these behaviors. That argues for consideration of combining multiple approaches such as their Smarter Pregnancy program, our website-based method, and greater emphasis by physicians and IVF nurse coordinators to achieve more impactful results.

The authors should be congratulated for this large effort to modify patients' behaviors with an intervention that is not resource intensive. Just as with the novel coronavirus, without data we are only left with assumptions that may well be erroneous. Although the impact on pregnancy was not evident, this trial generated a tested web-based resource for the many patients who are seeking guidance. It is not clear to us that a control group was helpful in this study because even filling out questionnaires could influence the behaviors being evaluated. We hope that this study and our commentary help to further such efforts.

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