Acupuncture—help, harm, or placebo?

David R. Meldrum, M.D.,[a] Andrew R. Fisher, B.S.E.,[b] Samantha F. Butts, M.D., M.S.C.E.,[c] H. Irene Su, M.D., M.S.C.E.,[d] and Mary D. Sammel, Sc.D.[e]

[a] Reproductive Partners Medical Group, Redondo Beach, California; [b] Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [c] Division of Infertility and Reproductive Endocrinology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [d] Division of Reproductive Endocrinology and Infertility, University of California, San Diego, California; and [e] Center for Clinical Epidemiology and Biostatistics, Philadelphia, Pennsylvania

The most recent meta-analysis appearing in *Fertility and Sterility* on acupuncture was reevaluated in view of the marked heterogeneity of interventions, controls, data analysis, and timing of interventions in the trials that were included. After removing some of the trials and data based on more rigorous standards for a high quality meta-analysis, a significant benefit of the intervention could no longer be shown. When studies with and without placebo controls were analyzed separately, a placebo effect was suggested. Individual trials with a confidence limit below unity emphasized the potential for a detrimental impact on outcomes, which should be considered both in using acupuncture clinically as an adjunct for IVF and in design of future trials. Much more data that includes a placebo control will be required before a conclusion can be made that acupuncture has a true treatment effect on IVF outcomes. However, unless the timing and method of the acupuncture are standardized, practitioners will still have difficulty being sure that their particular method will help beyond the apparent benefit provided by a placebo. (Fertil Steril® 2013;99:1821–4. ©2013 by American Society for Reproductive Medicine.)

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The first trial of acupuncture as an adjunct to improve IVF outcomes, which had a randomized control with no placebo treatment, was published more than 10 years ago in *Fertility and Sterility* by Paulus et al. (1). Since then our readers have had two major questions in mind: Could it be a placebo effect inclusive of the total acupuncture experience, the setting, and the providers?; and What is the magnitude of any purported effect? In the original trial by Paulus et al. (1), the odds ratio (OR) for clinical pregnancy was 2.08 (95% confidence interval [CI] 1.07–4.04). The trial therefore showed that at least a 7% improvement was observed (with 95% CI), but due to the relatively small trial (160 subjects), the actual benefit could have been more than fourfold. Because the control group had simply lain supine for the same period, a placebo effect could not be ruled out.

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Reprint requests: David R. Meldrum, M.D., Reproductive Partners Medical Group, 510 North Prospect Avenue, Suite 202, Redondo Beach, California 90277 (E-mail: drmeldrum@gmail.com).

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Placebo effects occur with many medical conditions and can be easily influenced by the attitudes of the investigative team. With the addition of acupuncture to the clinical protocol, the participating acupuncturists, who understandably believe that their acupuncture is effective, may have influenced other members of the health care team. It has become well accepted that a study control must be designed so that perceptions of all subjects are that they may be receiving active treatment (placebo control). In studies of acupuncture, the impact of a placebo can only be quantified by carrying out trials in which randomized controls undergo a similar procedure without insertion of needles. This mock acupuncture technique using a blunt Streitberger needle ("Streitberger control") has been widely recognized as the most reasonable control method for acupuncture studies, although that does assume that the mock acupuncture is not itself an active treatment

through pressure on the underlying tissues (acupressure). Paulus and his team promptly carried out a trial of similar size using the Streitberger control, which was unfortunately only published as an abstract (2), and as such the results were not widely disseminated. They found that the OR had diminished to 1.28 with a confidence interval that widely straddled 1 (95% CI 0.73–2.26), indicating a lack of statistical significance.

Since the original Paulus reports (1, 2), more trials on this intervention have been conducted, allowing for a closer estimate of the magnitude of effect through combining information from multiple studies into a single summary through a study design called meta-analysis. To have confidence that a particular intervention has a given magnitude of effect, a good meta-analysis combines data from studies with similar/the same populations, intervention, and outcomes. A meta-analysis is of higher quality if it contains only randomized controlled trials, particularly if there are valid, comparable placebo controls. Ultimately, the validity of a meta-analysis rests on the quality of the studies included in the analysis. When study designs vary widely, a meta-analysis of all studies may not be appropriate if results are too heterogeneous to allow meaningful combination of data.

Multiple meta-analyses have been published on randomized controlled trials of acupuncture, the most recent of which appeared in our journal in March of this year (3) and is the basis for this discussion. For 23 studies carried out on more than 5,000 subjects, the summary OR reported for clinical pregnancy rate (PR) was 1.22 (95% CI 1.01–1.47), with statistical significance barely being achieved. Although strengths of the study by Zheng et al. (3) included a comprehensive search of relevant studies, as well as sensitivity analysis on the use of the Streitberger control and timing of the intervention, we wish to highlight the heterogeneity among the studies and examine changes to the summary ORs for IVF outcomes when this variation in study design is considered. When the details of the individual studies are examined, there is a remarkable variation in the controls, acupuncture techniques (type of acupuncture, sites of application, manipulation of the needles, and application of ear seeds), the number of treatments, and the timing of the acupuncture in the IVF cycle.

First, the meta-analysis evaluation of clinical PR presented by Zheng et al. (3) included a cohort study that was not a randomized controlled trial (4). In addition, three trials had controls that were dissimilar to the remaining studies (alfentanil combined with a paracervical block [5, 6] or general anesthesia [7]). Both alfentanil and lidocaine reach the follicular fluid (FF) and a short exposure to lidocaine decreases mouse oocyte fertilization and embryo development (8), whereas, to our knowledge, the effects of alfentanil on oocytes and embryos have not been tested alone or in combination with lidocaine. The recalculated OR after removing those four trials is 1.24, with a CI that touches 1 (95% CI 1.00–1.54).

Second, in three studies Zheng used data combined from multiple arms (9–11). The OR for clinical PR after using only pure acupuncture and control arms was 1.19 (95% CI 0.98–1.44). Third, in another trial, "special Chinese medical drug" seeds were held on the ear for 2 days and pressed for 10 minutes each day, making the treatment arm acupuncture plus drug (12). If that trial is removed and the multiple arm studies are appropriately modified so that only a single acupuncture arm and control are included, the CI for clinical pregnancy crosses 1.0 (OR 1.14; 95% CI 0.94–1.37), indicating lack of a significant benefit of acupuncture.

Fourth, an attempt was made to analyze subsets of trials based on timing of the intervention (e.g., acupuncture done around the time of transfer). Even after excluding studies with Streitberger controls, no statistically significant differences were noted in these smaller subgroups. Furthermore those groupings were not distinct (e.g., studies "around ET" included data where acupuncture was also done on day 9 of stimulation (13) or 2 (14) or 3 (12) days after ET). We are not much closer to having a more accurate estimate of the magnitude of the effect (placebo or otherwise) of any particular timing of acupuncture. The sole study that reproduced the original Paulus study (1) with more subjects (225) found only a 30.3% clinical PR with acupuncture compared to 33.8% with no treatment (15).

Important, when the six studies using the Streitberger control were combined, the OR for clinical pregnancy was 0.89 (95% CI 0.73–1.09). For three of those studies reporting births (2 studies were by the same investigators), the OR was significantly reduced at 0.74 (95% CI 0.58–0.95). The reduced chance of birth suggests a detrimental effect of acupuncture, unless the mild acupressure of the Streitberger control produced a treatment effect superior to any effect of needle placement. If we were to accept the latter hypothesis, all acupuncture should cease and acupressure similar to the Streitberger control should take its place.

There may be a more rational explanation for the reduced outcome in the studies showing lower PRs and delivery rates with acupuncture. Under certain circumstances, acupuncture could actually be harmful. This is of much greater importance than attempting to show a benefit. There were two individual studies that produced statistically significant results with an OR of less than 1. So et al. (16) randomized 370 patients achieving an OR for clinical pregnancy of 0.66 (95% CI 0.44–0.99). In that study, manipulation of the needles was described as "rotating, lifting, and thrusting." In the other study (Craig, personal communication), the acupuncture group had not previously experienced the acupuncture or the provider and had to be transported across town on the day of ET for the acupuncture to be carried out. The OR was 0.34 (95% CI 0.15–0.79) (17). It is entirely plausible that acupuncture, particularly if applied aggressively or in a patient unaccustomed to the treatment and acupuncturist, could have a negative effect by causing stress during a critical time of the IVF cycle. Reanalysis without those studies no longer reveals a negative impact of acupuncture.

It has been argued that a placebo effect should not occur with acupuncture because pregnancy is objective, rather than a subjective outcome, like pain (3, 18). However, a large analysis of placebo effects has clearly documented that objective, physical end points are influenced by placebos (19). A recent study even showed that the placebo effect can be documented (at least with the subject symptom complex, irritable bowel syndrome) when the subjects are told they