MOXI trial—is it time to stop routinely recommending antioxidant therapy to infertile men?

Nutraceutical therapy—and more specifically antioxidant supplementation (AoS)—has a special place in male reproductive medicine. Even before DNA fragmentation and reactive oxygen species testing became more widely available, we have been leading our patients to the edge of the tangled forest that is the over-the-count supplement market. We have done this in good faith—based on level 1 evidence (albeit with methodological problems) and as a relatively innocuous last-ditch therapy for those men whose evaluation failed to reveal an opportunity for targeted hormonal or surgical therapies. Although the risks are minimal, the burdens of cost and convenience, and the unanswered questions of efficacy have long begged for high-quality evidence. Even as the recent Cochrane Review (1) showed a modest benefit in pregnancy rates from AoS, and it prominently cited the historically poor quality of evidence included in their analysis. The study by Steiner et al. (2) sought to address the basic questions related to the real-world fertility effects of AoS in an adequately powered, randomized double-blind placebo-controlled trial.

Steiner et al. (2) examined the efficacy of a commercially available antioxidant combination pill as a treatment for infertile men with abnormal semen parameters. They examined changes in semen parameters, including DNA fragmentation, after several months of treatment. They also evaluated natural and intrauterine insemination pregnancy rates. The latter was offered only after the couples failed to conceive after 3 months. The trial—Males, Antioxidants, and Infertility (MOXI)—reflected the efforts of multiple institutions and resulted in 144 men completing the trial. The investigators controlled for cross-over by assaying serum antioxidant levels in both groups. The results were sobering—there was no beneficial change in bulk semen parameters (concentration, motility, or morphology) nor any significant change in sperm DNA fragmentation indices. Interestingly, sperm concentration actually worsened after antioxidant supplementation when compared with placebo. They also did not find any difference in pregnancy (both by natural means or intrauterine insemination with ovulation induction) or live birth rates; however, the trial was not powered for these particular end points. The investigators concluded that AoS (in this form, at least) did not have a meaningful impact on the most relevant outcomes for infertile men.

DNA fragmentation is a test without a reliable treatment—what can we do for an infertile man with an abnormal value? These findings have left us with only surgical interventions to address this clinical finding—varicocelectomy or surgical sperm retrieval. Now we can state that, based on the sperm chromatin structure assays in this trial, AoS should not be offered to address abnormal DNA fragmentation while men are attempting to conceive naturally or by way of intrauterine insemination. It would have been interesting to analyze whether men with abnormal oxidative stress adduct assays benefited from antioxidant therapy.

Steiner et al. (2) selected the supplements vitamin E, selenium, *N*-acetylcysteine, and carnitine as their intervention. This reflects a readily available commercial formulation. Although at a certain point all trials must make such a choice, it would have been interesting to see coenzyme Q10 evaluated as an intervention. Coenzyme Q10 also has promising Level 1 evidence supporting its ability to improve sperm concentration and motility (3).

Certainly there are some theoretical possibilities that would explain the absence of beneficial results from AoS in this trial. The formulation chosen may not have been appropriate. There were more men with secondary infertility in the placebo group. The study excluded men with severe oligozoospermia. The usual limitations of prospective trials aside, this study is a very compelling argument to save our patients the cost and burden of empiric therapy with over-the-counter antioxidant nutraceuticals.

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