So near yet so far away

There is much to admire about the article recently published in *F&S Reports* by Matorras et al. (1) highlighting the positive impact of vitamin E therapy on live birth rate per transfer in an assisted reproductive technology setting, although no changes were observed in conventional semen parameters such as sperm motility and morphology. The experimental design of this study involved the randomized treatment of patients with either vitamin E (400 mg/d) or an identical placebo tablet for 3 months in a blinded fashion. The sample size calculations and statistical analysis (Kolmogorov-Smirnov test followed by analysis of variance) were all exemplary and the overall purpose of the study, to evaluate the clinical effectiveness of antioxidant therapy in an in vitro fertilization setting, entirely laudable. However, there is a flaw – and it is a fatal one.

The patients enrolled in this treatment were defined by male factor infertility (65.5%), tubal factor (13.5%), endometriosis (8.8%), and idiopathic infertility (22.1%), making a total of 109.9%, which reflects, presumably, the existence of comorbidities within this infertility cohort. Looking at these entry criteria, it is difficult to imagine how giving antioxidants to the male partner of an infertile couple is going to help, if tubal occlusion or endometriosis is the cause of their distress. Furthermore, even if the infertility does involve male factors, or is simply idiopathic, these generic conditions are known to involve many possible causes, only one of which is oxidative stress. Therefore, this is a clinical trial that is set up to fail. It is like giving insulin to everyone coming into hospital in a coma; some will exhibit a miraculous recovery, some will die, and, overall, any therapeutic benefit will be lost in the noise.

Clinical trials of antioxidant therapy have to begin with the identification of oxidative stress in the patient. If you give powerful antioxidants to a patient with no sign of such stress, you will create a state of redox imbalance that will culminate potentially in reductive stress, which is just as bad as its oxidative counterpart when it comes to the disruption of normal sperm function (2). In animal models exhibiting a definitive post-testicular oxidative stress (as observed in the glutathione peroxidase 5 knock-out mouse, for example) we already know that antioxidant treatment effectively will restore reproductive function to complete normality (3). Unfortunately, in human antioxidant trials, the selection of patients on the basis of oxidative stress has rarely, if ever, been attempted. What trials have been conducted either use no selection criteria at all, as in this study, or the patients have been selected on the basis of defects in the semen profile, most commonly asthenozoospermia. Of course, we all recognize that oxidative stress dramatically can impair sperm motility, however, it is not the only factor capable of causing this condition; a range of genetic, clinical, and environmental factors that have nothing to do with oxidative stress are capable also of effectively delivering an asthenozoospermic phenotype (4).

There are several clinical studies where the contemporaneous measurement of oxidative stress markers, such as malondialdehyde, clearly has demonstrated the therapeutic potential of antioxidant therapy (5). However, even in these studies, malondialdehyde has not been used as a patient selection criterion. Indeed, it could be argued that we should not even begin such expensive, time-consuming clinical trials until we have developed, validated, and agreed on a robust biochemical marker of oxidative stress, such as malondialdehyde, 4-hydroxynonenal, or 8-Oxo-2′-deoxyguanosine (8oxodG), as the key patient selection criterion. We should then ascertain whether our antioxidant mixture of choice has the capacity to reduce levels of oxidative stress according to the same diagnostic markers that we used for patient selection. If this is the case then, and only then, can we really ask valid questions about the impact of such therapy on semen quality or even pregnancy.

Although the study by Matorras et al. (1) encourages the belief that changes in live birth rate per transfer ultimately might be observed following antioxidant treatment, simply reducing the expression of 8oxodG in the spermatozoa should be sufficient reason to support such therapy, given this metabolite's capacity to induce mutational change in the offspring. If a reduction in 8oxodG was observed in such trials, then we would have a clear rationale for using antioxidants in oxidatively stressed patients to ensure that the gametes that we are bringing into close proximity in the name of assisted reproductive technology are of the best possible quality. Such a strategy really should be incorporated into our therapeutic armamentarium as a matter of "best practice" to minimize any risk to the health and well-being of the progeny as a consequence of using assisted conception procedures.

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