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LETTER TO EDITOR

Reply: antioxidant trials—the need to test for stress

Sir,

We thank Professor Aitken (Aitken 2021) for his interest in our published study on role of antioxidants prior to ART in male subfertility.

We agree with Professor Aitken's assertion that there is no validated test yet of reliably measuring antioxidant stress in seminal fluid. He makes a very valid example of using insulin in coma—in other words, there might be a subpopulation that would benefit but a subpopulation that might in fact be harmed by the intervention. Therefore, until such time as valid tests are available and antioxidants are tested in randomized controlled trials (RCTs), the blanket use of antioxidants for male subfertility should be discouraged due to the potential harm it could inflict on some couples with male factor infertility.

However, it is debatable whether there is a need to conduct trials evaluating effectiveness of antioxidants for male subfertility before a valid test for measuring oxidative stress is available. As correctly highlighted by Professor Aitken, the use of antioxidant as an "add on" prior to ART is a common practice, even though there is paucity of high quality evidence (Kamath *et al.*, 2019). Even the recent Cochrane update on antioxidants reported only two RCTs evaluating antioxidants prior to ART (Smits *et al.*, 2019). Due to persistent knowledge gap, we planned an RCT to address a largely under investigated intervention in the given clinical scenario, in other words, prior to assisted reproductive technique-intracytoplasmic sperm injection (ART-ICSI). It might be relatively simpler to plan an RCT which includes only sub fertile men with documented oxidative stress as the antioxidant therapy may show a greater benefit (larger effect size) and consequently may require a smaller sample size. However, this would not reflect current clinical practice, especially prior to ART-ICSI for male subfertility where role of currently available DNA fragmentation test is limited. The current pragmatic trial was planned to reflect the contemporary clinical practice which, in our view, is the first step toward clearing the ambiguity on the role of antioxidants prior to ART in male factor subfertility. While weaknesses in the execution of the trial precluded any definitive conclusions from the current trial, pooling of dataset through individual participant data (IPD) could help in providing definitive answer in the future. A large double-blind placebo-controlled trial might be ideal for unselected population of sub fertile men, but there would be methodological constraints in practice.

As it is increasingly clear that indiscriminate use of antioxidants without oxidative testing is not beneficial for male subfertility (Schisterman *et al.*, 2020; Steiner *et al.*, 2020), the next step is to standardize the test for oxidative stress and identify the population which may benefit from the intervention. This standardization is essential considering the lack of consensus on which test for oxidative stress or DNA fragmentation to use in clinical practice. The variation reported between some tests for DNA fragmentation (Chohan *et al.*, 2006) and temporal variation (such as diurnal variation (Ni *et al.*, 2019)) in results in the same individual are issues that need to be addressed. At present DNA fragmentation testing is not recommended prior to fertility treatment by professional bodies (Practice Committee of the American Society for Reproductive Medicine, 2013).

Finally, we disagree with using antioxidant stress markers as a primary endpoint. The primary endpoint of any RCT in reproductive medicine should be the live birth rate as that is the primary outcome of concern to both clinicians and patients. Antioxidant stress markers may be used as secondary endpoints to describe the mechanistic effects of the therapy used, but cannot be taken as the primary index of therapeutic efficacy. And it is important that consistent end-points be used in RCTs in reproductive medicine to enable better comparability between trials and better translatability of research findings into the clinical context (Duffy *et al.*, 2020).

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