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Platinum Priority – Editorial

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Empiric Medical and Nutritional Therapy for Idiopathic Male Infertility: How Good Is the Evidence for What Works and Does Not?

Joseph Y. Clark *

Division of Urology, Department of Surgery, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

Globally, it is estimated that infertility affects approximately 15% of couples and the infertility attributable to males ranges between 20% and 70%, with a male factor involved in approximately half of cases in North America and Europe [1]. In one study of infertile men referred to an andrology clinic, after eliminating known causes of infertility, 44% of the men were classified as having idiopathic infertility and the vast majority of these men had impaired semen quality [2].

Many empiric therapies have been investigated in attempts to improve the semen parameters in this subset of men, with the hope that ultimately these therapies would result in pregnancies and live births. In this issue of *European Urology*, Omar et al. [3] report a systematic review and meta-analysis of clinical trials comparing drug and nutritional therapy to improve pregnancy and live birth rates, and semen parameters in men with idiopathic infertility.

Their meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines, searching electronic databases from January 1990 to September 2017. After exclusions, 61 English language articles were selected, all but two of which were randomized controlled trials. There was some evidence of improvement in some semen parameters with pentoxifylline, co-enzyme Q10, L-carnitine, follicle stimulating hormone, tamoxifen, and kallikrein. The authors concluded that there is some evidence that empiric medical and nutritional therapy may improve semen parameters.

Although there are other recent systematic reviews summarizing the evidence on the effects of medical therapy [4,5], nutritional supplements [6,7], and both [8] on idiopathic male infertility, this is the first comprehensive

review of the impact of both nutritional and medical therapy on male infertility to use the Cochrane Collaboration's tool for assessing risk of bias (RoB) in randomized trials [9] and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess evidence quality. The GRADE system rates the quality of evidence and grades the strength of recommendations [10].

The studies by Salas-Huetos et al. [6] and Showell et al. [7] were the most rigorous in that they did use the RoB tool; however, when comparing these two reviews with the current one, even for the exact same study, there were some differences in the RoB assessment, indicating that there is some subjectivity even among experienced investigators reviewing and extracting data. In addition, depending on the inclusion and exclusion criteria for selection of studies to review, a different panel of studies was used for the analysis; for instance, the study by Showell et al. included foreign language (non-English) publications and language experts were recruited to assist with translation. Despite these differences, the conclusion of the authors of this review [3] as well as the other reviews [6,7] was that there was some evidence that the listed interventions improved semen parameters.

Although meta-analysis is a powerful statistical tool for summarizing knowledge in a research field and assessing a treatment effect, there are several areas where personal judgment and expertise come into play, most importantly in quality assessment of the study. Other factors to take into consideration when assessing the results of a meta-analysis include the heterogeneity between studies and publication bias; both of these limitations were mentioned in the article, but to clarify, publication bias, the phenomenon

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* Division of Urology, Penn State Hershey Medical Center, 500 University Drive, Hershey, PA 17033, USA. Tel. +1 717 5318848; Fax: +1 531 5314475. E-mail address: jclark13@pennstatehealth.psu.edu.

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whereby positive results are more likely to be submitted to journals and more likely to be published than negative results, is a significant potential source for a type I error. In addition, the I^2 statistic for most of the meta-analyses approached 100% and the forest plots show little overlap between the confidence intervals, indicating high heterogeneity. Therefore, the results of this present meta-analysis showing “some evidence that empiric medical and nutritional supplements may improve semen parameters” should be interpreted with caution since the certainty of evidence was judged as “very low”. The authors rightfully admit that there is very limited evidence that empiric therapy leads to higher rates of pregnancies or live births.

Despite the soft conclusions, this is a much-needed review and meta-analysis on nutritional supplements and drugs to treat idiopathic male infertility using RoB assessment and the GRADE system. The authors note the limitations of the review, including the fact that most of the studies reported on changes in semen analysis parameters with the intervention, with only a few reporting live birth rates. It should be kept in mind that small to moderate improvements in semen parameters do not necessarily result in higher rates of live births. The value to the reader is that empiric therapies can be considered, but be used with caution and only after appropriate counseling. This comprehensive, statistically sound review and meta-analysis underscores the need for properly powered, well-designed, prospective, randomized, placebo-controlled trials using medical and nutritional therapies, with semen parameters, pregnancy, live birth rates, and female partner conditions reported.

Future trials should consider incorporating data on lifestyle stressors, diet, physical activity, body habitus, and even sleep disturbance [11–13], as these have all been implicated in male infertility. This is a monumental task but the weak evidence in the current literature as summarized in this review should spur researchers to collaborate in enrolling patients in clinical trials of agents that hold the most promise, determine strict inclusion and exclusion criteria with proper randomization, and set primary and secondary endpoints to include live birth rates. An additional benefit of a large, comprehensive trial is that a subset of men may be identified who could benefit from medical and/or nutritional therapy. As the current systematic review was undertaken under the auspices of the European Association of Urology, perhaps the same organization can also spearhead and coordinate such a prospective trial that could show the evidence of what is effective in idiopathic male infertility.

Conflicts of interest: The author has nothing to disclose.

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