Reply of the author to "real world evidence"

The investigators have provided additional commentary regarding their observations on preoperative preparation of somewhat hypogonadal men for sperm retrieval surgery. The definition of hypogonadism in this manuscript is more liberal than that provided by the American Urological Association, the Endocrine Society, or other authorities on hypogonadism. Interpretation of the manuscript is limited because details of the study were not provided in the published article. It is critical for an article to describe exactly how the study is done for the data to be repeatable and verifiable by other investigators.

Of greatest concern is the allocation of men to treatment or no treatment. Of the 616 men reported in this study, 291 did not receive medical treatment for their "low" testosterone. Why did they receive or not receive treatment? This was not a randomized trial, and allocation of patients to treatment can dramatically influence results of the study. The method of allocation (apparently decided by patients) can create substantial biases for interventional trials, affecting the results of the study.

The second concern is the repetition of a semen analysis on the day of sperm retrieval, where up to 10% of men with presumed nonobstructive azoospermia (NOA) will have rare sperm found, as presented in a commentary on the article (1). It is particularly important to perform these studies on men with maturation arrest and/or hypospermatogenesis, a substantial proportion of the men who "responded" to treatment and had sperm found with surgical retrieval. However, the process of repeat semen analysis is not mentioned in the methods section of the article, only that sperm were frozen when detected in the ejaculate. This is a critical detail of patient management when it was done actually in the management of these patients. Once again, the methods section of an article must include such critical details, not to provide ad hoc information after the article has been accepted for publication and raise questions about the entire validity of the published study.

The use of human chorionic gonadotropin (hCG) for men before attempted sperm retrieval remains an unfounded and unsupported intervention that has not been shown to increase sperm retrieval in studies with high-level evidence. As Esteves et al. (2) point out in their letter to the editor, the patients who "responded" to hCG were those men who already had better overall spermatogenesis, i.e., those with lower follicle-stimulating hormone (FSH, 4.0 IU/L) level. In our experience, this is a subgroup of patients with presumed NOA who often have sperm in the ejaculate with a more detailed, extended sperm preparation, so surgery is an unnecessary intervention. The use of hCG to suppress FSH levels, a hormone that functionally stimulates sperm production, remains an unfounded intervention. There is no scientific evidence to support the hypothesis of Sertoli cell receptor desensitization from high circulating FSH levels that the investigators propose.

Taken together, the data in this manuscript must be considered with great caution. "Real World Evidence" is not high-quality scientific evidence. The publication of a series of patients variably selected for treatment and observed for results of sperm retrieval does not provide reliable evidence to support presurgical hormonal therapy or varicocele repair. In my opinion, the evidence-based conclusions clearly presented in the American Urological Association and American Society for Reproductive Medicine joint guidelines for male infertility (3) stand as published; there is no scientific evidence for varicocele repair or hormonal therapy before sperm retrieval in men with NOA.

CRediT Authorship Contribution Statement

Peter N. Schlegel: Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Conceptualization.

Declaration of Interests

P.N.S. has nothing to disclose.

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https://doi.org/10.1016/j.fertnstert.2024.08.348

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