To the editor: understanding presperm retrieval hormonal treatment effectiveness in nonobstructive azoospermia through real-world evidence

We thank Schlegel (1) for his editorial accompanying our manuscript (2). We understand the importance of high-quality evidence in guiding clinical practice and believe that it is necessary to address the points raised.

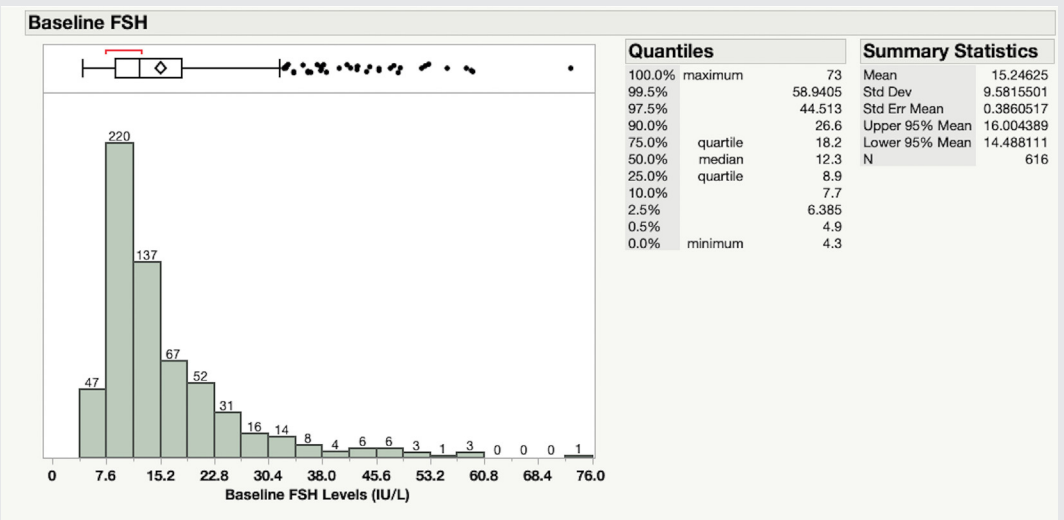
Randomized controlled trials (RCTs) and real-world evidence (RWE) studies contribute to understanding the effectiveness of medical interventions. Real-world evidence is particularly valuable in complex clinical scenarios where RCTs may not always be feasible. Our RWE study of 616 infertile men with nonobstructive azoospermia (NOA) and biochemical hypogonadism found that hormonal therapy and the absence of clinical varicocele were associated with improved microdissection testicular sperm extraction (micro-TESE) success. These findings offer potential insights that future RCTs with well-characterized study populations and standardized interventions may support (3).

The editorial cites a study that found no benefit from medical therapy on sperm retrieval rates (SRRs) (4). However, our study differed in design, patient population, and treatment protocols. We used a testosterone cutoff of 350 ng/dL to define hypogonadism, as endorsed by most societies, whereas that study used 300 ng/dL, indicating more pronounced Leydig cell insufficiency, possibly less responsive to therapy. Although the SRR was nominally higher (61% vs. 51%, $P=.31$) for men who received no therapy, the cited study was underpowered with only 41 untreated patients, raising questions about whether the treatment regimen was optimal.

Concerns about misclassifying patients with NOA are unfounded. All patients followed a stringent NOA diagnosis protocol with histopathological confirmation. The interquartile baseline follicle-stimulating hormone (FSH) level ranged from 8.9 to 18.2 (Fig. 1). Only 47 patients (approximately 8%) had FSH levels of <7.6 IU/L, consistent with the seminal study by Schoor et al. (4); these patients mainly had idiopathic NOA (80.1%) and maturation arrest (75%).

Criticism of limited data on patient evaluation and management before micro-TESE is inaccurate. Confirmatory semen analyses corroborated the azoospermia diagnosis and checked on the day of micro-TESE. Patients with viable sperm in the ejaculate were excluded, as shown in the supplemental flowchart. The hormonal therapy algorithm was detailed and illustrated (Fig. 2).

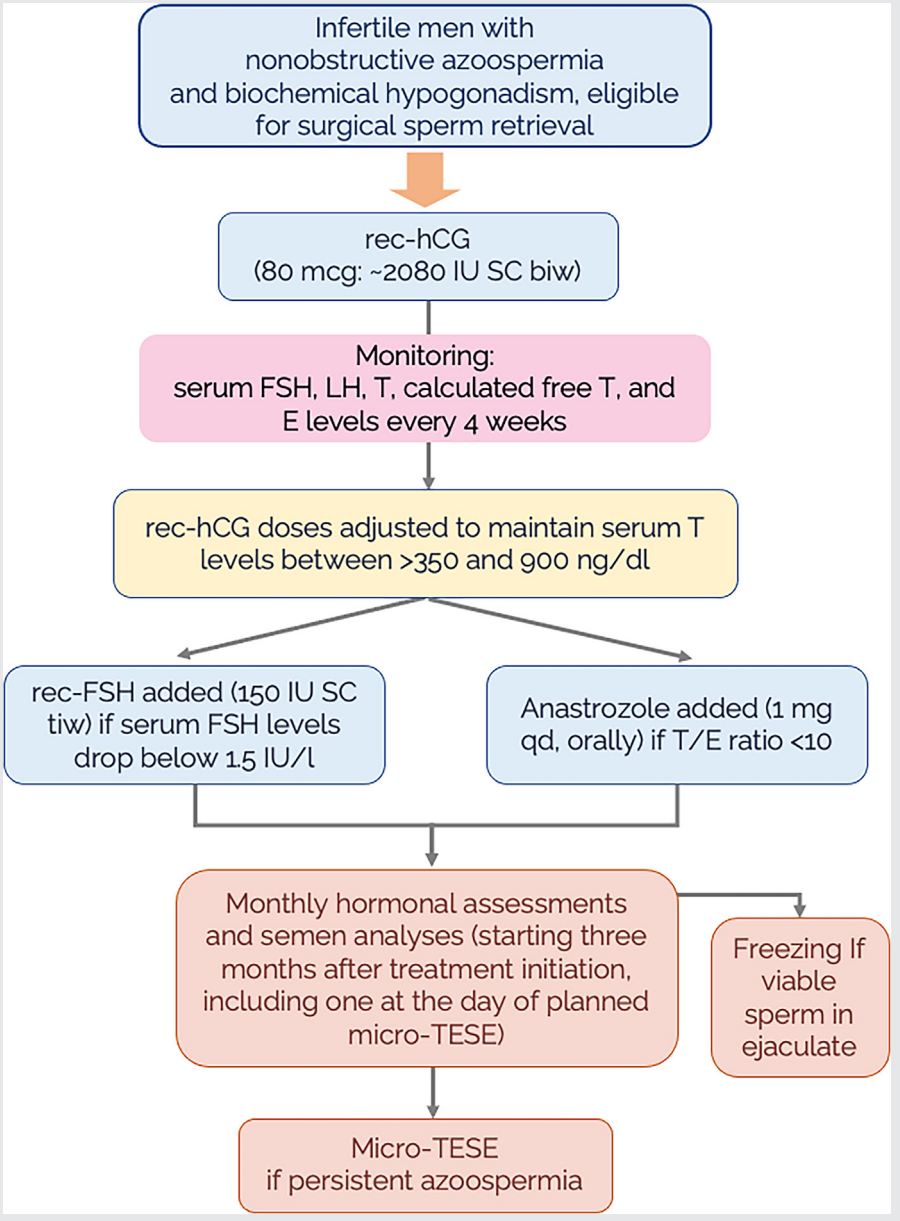
FIGURE 1



Histogram and box plot showing the distribution of baseline serum follicle-stimulating hormone (FSH) levels in the study population (n = 616). The horizontal axis scale shows the baseline FSH levels in increments of 7.6 IU/L (bins). The number of patients in each bin is shown on *top* of each bar. The box plot shows the median for the data in the *center line*. The *left* and *right* borders of the box show the 25th and 75th quantiles. The whiskers represent the variation of the data (minimum and maximum values, excluding outliers). The outliers, representing values over 1.5 times the interquartile range, are shown as red dots outside the right whisker. The middle of the diamond is the population mean, and the extremities of the diamond are the 95% confidence intervals of the means. The red bracket on *top* of the box indicates the shortest half (the most dense 50%) of the observations. The tables show the quantile values and summary statistics. Std Dev = standard deviation; Std Err Mean = standard error of the mean.

Esteves. Letter to the editor. Fertil Steril 2025.

FIGURE 2



Algorithm for hormonal therapy before microdissection testicular sperm extraction (micro-TESE) used in our study (2). The figure illustrates the hormonal stimulation protocol, which entails the off-label use of human chorionic gonadotropin (hCG) alone or combined with follicle-stimulating hormone (FSH). Patients received subcutaneous injections of recombinant human chorionic gonadotropin (rec-hCG; choriogonadotropin alfa, 250 μg/0.5 mL, prefilled pen for injection) at a dose of 80 μg (equivalent to approximately 2,080 IU) twice weekly. Dosage adjustments were made as necessary to maintain the total testosterone (T) levels between >350 and 900 ng/dL. If the serum FSH levels decreased to <1.5 IU/L during rec-hCG stimulation, patients also received recombinant FSH (rec-FSH; follitropin alfa, 300 IU/0.5 mL), using a prefilled multidose pen at a dose of 150 IU 3 times a week, in conjunction with rec-hCG therapy, for at least 3 months. An aromatase inhibitor (AI) was prescribed off-label if the ratio of T (ng/dL) and estradiol (E; pg/mL) decreased to <10 during hCG therapy. The AI was administered orally (1 mg daily) to maintain the T/E ratio above 10. Monthly monitoring included hormone measurements (serum FSH, luteinizing hormone [LH], E, T, and free T), with liver enzyme measurements for those taking AIs. Semen analysis was performed periodically, starting 3 months after treatment initiation and then every 4 weeks for patients continuing therapy for over 3 months, including an assessment on the day of planned micro-TESE. If viable sperm were detected in any semen analysis, sperm cryopreservation was performed; otherwise, patients underwent micro-TESE after at least 3 months of treatment. biw = twice weekly; qd = once a day; SC = subcutaneously; tiw = thrice weekly.

Esteves. Letter to the editor. Fertil Steril 2025.

The editorial questions using human chorionic gonadotropin (hCG) over selective estrogen receptor modulators and aromatase inhibitors to boost testosterone production. We believe that hCG is advantageous because it not only boosts testosterone production but also suppresses the FSH levels and, therefore, may counteract Sertoli cell receptor desensitization from high circulating FSH levels. This contrasts with selective estrogen receptor modulators and aromatase inhibitors, which increase already elevated FSH levels, potentially causing further FSH receptor desensitization. In our study, FSH remained within physiological levels in approximately 60% (172/291) of hormone-treated patients. Only 20% (59/291) experienced marked suppression, necessitating FSH supplementation. We found that premicro-TESE FSH levels were lower in patients with positive outcomes (4.0 IU/L; 95% confidence interval, 2.9–7.6) than in those with failed retrievals (8.1 IU/L; 95% confidence interval, 5.4–15.0; $P<.0001$), supporting the idea that hCG may improve Sertoli cell function by counteracting FSH receptor desensitization (5).

The editorial finds our observation of lower SRRs in men with clinical varicocele interesting but cites a small series of 31 men that found no effect of varicocele on SRRs. However, our findings align with most published series, which collectively suggest that the presence of varicocele is linked to lower SRRs and that testicular function improvement is achievable after varicocele repair.

In conclusion, although our study does not replace RCT evidence, it provides significant insights into managing hypogonadal men with NOA. We advocate for a balanced approach that considers both RWE and rigorous clinical trials to guide patient care.

CRediT Authorship Contribution Statement

Sandro C. Esteves: Conceptualization, Writing – original draft, Writing – review & editing. Arnold P. P. Achermann: Writing – review & editing. Cassio L. Z. Riccetto: Writing – review & editing.

Declaration of Interests

S.C.E. reports receipt of unrestricted research grants from Merck KGaA (Germany); honoraria for lectures from Merck KGaA and Med.E.A. (Italy); WHO Topic Leader, Male Infertility Group, WHO Infertility Guidelines, unpaid; Brazilian Society of Human Reproduction, Andrology Committee Coordinator, unpaid; and Medea Member, Reproductive Medicine Committee, unpaid. A.P.P.A. has nothing to disclose. C.L.Z.R. has nothing to disclose.

Sandro C. Esteves, M.D., Ph.D.[a,b]
Arnold P.P. Achermann, M.D.[a,b]
Cassio L.Z. Riccetto, M.D., Ph.D.[b]
[a] ANDROFERT, Andrology and Human Reproduction Clinic, Campinas, Brazil; [b] Division of Urology, Department of Surgery, State University of Campinas (UNICAMP), Campinas, Brazil

https://doi.org/10.1016/j.fertnstert.2024.08.318

REFERENCES

1. Schlegel PN. Commentary on factors affecting microsurgical testicular sperm extraction success. Fertil Steril 2024; https://doi.org/10.1016/j.fertnstert.2024.07.040.
2. Esteves SC, Achermann APP, Miyaoka R, Verza S Jr, Fregonesi A, Riccetto CLZ. Clinical factors impacting microdissection testicular sperm extraction success in hypogonadal men with nonobstructive azoospermia. Fertil Steril 2024; https://doi.org/10.1016/j.fertnstert.2024.06.013.
3. Esteves SC, Humaidan P, Ubaldi FM, Alviggi C, Antonio L, Barratt CLR, et al. APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function. Reprod Biomed Online 2024;48:103647.
4. Schoor RA, Elhanbly S, Niederberger CS, Ross LS. The role of testicular biopsy in the modern management of male infertility. J Urol 2002;167:197–200.
5. Foresta C, Bettella A, Spolaore D, Merico M, Rossato M, Ferlin A. Suppression of the high endogenous levels of plasma FSH in infertile men are associated with improved Sertoli cell function as reflected by elevated levels of plasma inhibin B. Hum Reprod 2004;19:1431–7.