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EAU Guidelines View

Varicocele Treatment in Azoospermia Before Artificial Reproductive Techniques: Critical Considerations by the EAU Guidelines Panel on Sexual and Reproductive Health

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A clinical varicocele is found in ~15% of men in the general population and in ~11% of those with nonobstructive azoospermia (NOA) [1]. Although substantial evidence supports the benefits of varicocele repair in infertile men—particularly in terms of improvements in sperm concentration and higher pregnancy rates—its efficacy in men with NOA remains highly debated [2]. Furthermore, while the exact pathophysiological mechanisms underlying the effects of varicocele repair in NOA are not fully elucidated, it is hypothesized that spermatogenesis and sperm function may be stimulated or restored via a reduction in oxidative stress and enhancement of testosterone production [3]. Although unlikely, these changes may result in the reappearance of sperm in the ejaculate at concentrations sufficient to permit spontaneous conception or to facilitate the use of less invasive assisted reproductive technologies (ARTs). Alternatively, such changes could enhance the success rates of testicular sperm extraction (TESE) and improve live birth outcomes following TESE-intracytoplasmic sperm injection (ICSI) cycles.

Over the past two decades, several studies—predominantly observational and retrospective—have investigated this controversial topic, including five systematic reviews and meta-analyses. A 2024 meta-analysis of nine controlled studies (six retrospective and three randomized trials) assessed the impact of varicocele repair on sperm recovery in men with NOA [4]. The appearance of sperm in the ejaculate following varicocelectomy ranged from 17.8% to 62.5%, in comparison to 0–25% for untreated men. Significant improvements were also observed in sperm concentration (standardized mean difference [SMD] 1.81, 95% confidence interval [CI] 0.84–2.77; $p < 0.001$), progressive motility (SMD 4.28, 95% CI 2.34–6.22; $p < 0.001$), and morphology (SMD 3.59, 95% CI 2.27–4.92; $p < 0.001$) among men with sperm present after repair in comparison to those who did not undergo surgery. However, the studies included were of low methodological quality, exhibited high heterogeneity, and did not report pregnancy outcomes. A recent meta-analysis comparing 269 men with NOA who underwent varicocelectomy before TESE to 364 untreated men demonstrated a significantly higher surgical sperm retrieval rate (SRR) in the varicocelectomy group (odds ratio [OR] 2.17, 95% CI 1.17–4.01; $p = 0.01$). Varicocele repair also increased the likelihood of sperm appearing in the ejaculate (OR 7.80, 95% CI 3.59–16.94; $p < 0.001$) and improved clinical pregnancy rates following ICSI (OR 2.18, 95% CI 1.03–4.60; $p = 0.04$) [2].

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These quite limited clinical data suggest that varicocelectomy may offer a viable approach for improving or inducing spermatogenesis in NOA patients, and could potentially facilitate pregnancy or enhance the testicular SRR for ART. It is crucial to emphasize that NOA does not represent a single disease entity, but rather an epiphenomenon of diverse underlying conditions, often with distinct genetic origins [5]. Adding further complexity to the scenario, the evidence available suggests that both absolute azoospermia and cryptozoospermia may exhibit temporal variability [6]. Current estimates suggest that a genetic etiology accounts for more than half of idiopathic complete azoospermia cases. Consequently, NOA patients exhibiting meiotic arrest or Sertoli cell–only syndrome (SCOS) are unlikely to benefit from varicocelectomy, as the primary pathological defect will not be corrected by treating a varicocele.

Clinically relevant progress in male reproductive genetics has been achieved via the introduction of multigene panels to screen for monogenic variants associated with NOA. Pathogenic variants in genes essential for spermatogenesis are detected in ~20% of men with NOA with chromosomal abnormalities or Y-chromosome azoospermia factor microdeletions [7]. Therefore, future randomized trials involving genotyped NOA patients with concomitant varicocele are essential to determine whether varicocelectomy has a role in this highly specific clinical subgroup.

NOA results from intrinsic testicular failure with disrupted spermatogenesis, often accompanied by primary hypogonadism, small testes, and impaired Leydig cell function [1]. Normally, luteinizing hormone stimulates Leydig cells to produce intratesticular testosterone (ITT), which activates Sertoli cells to support germ cell development. In NOA, Leydig cell insufficiency reduces testosterone, which worsens ITT deficiency and spermatogenic failure. Approximately 50–80% of NOA patients have biochemical hypogonadism with low serum testosterone [8]. Hypogonadal men exhibit higher SCOS rates and lower SRR than eugonadal men, which indicates that adequate testosterone is crucial for sperm recovery [8].

Hypogonadism also causes systemic effects—low bone density, fatigue, reduced libido, and metabolic issues—that are common in NOA. Thus, hormonal assessment is essential for patient counseling and for planning interventions, including hormonal stimulation and varicocele repair. However, no randomized long-term studies have confirmed the role of varicocelectomy in the protection of androgenic function in the testis. It remains unclear whether improving ITT via varicocelectomy in monogenic NOA alters Sertoli or stem cell function to restore spermatogenesis and enhance TESE outcomes. Future research should use exosome or genome sequencing to identify genetic defects and stratify NOA patients in the trial setting [9].

Taken together, these observations indicate that the role of varicocelectomy in this context remains controversial owing to the paucity of randomized trials and marked heterogeneity among studies included in meta-analyses. A recent global survey revealed significant variation in practice, with 57.7% of urologists recommending varicocelectomy for men with NOA and a clinically palpable varicocele [10]. International guidelines reflect this debate: the EAU 2025 guidelines on sexual and reproductive health [1] acknowledge that varicocele repair in NOA may lead to sperm reappearance in the ejaculate, but emphasize the low quality of evidence and provide only a weak recommendation. Conversely, the American Urological Association/American Society for Reproductive Medicine 2024 guidelines offer no definitive recommendation (expert opinion), and stress individualized decision-making after appropriate counseling [11].

Overall, despite encouraging findings, several caveats remain, notably timing. Ejaculated sperm typically appear within ~3–9 mo after varicocelectomy, which corresponds to one or more spermatogenic cycles. Delaying TESE beyond two cycles may be potentially harmful, as postponing effective NOA treatment (microTESE) may negatively impact on the chances of successful pregnancy because of a decline in the female partner's ovarian reserve.

Furthermore, the question arises as to whether repair should be limited to men with favorable histology, and possibly linked to genetic abnormalities. Diagnostic biopsy may expose men to unnecessary procedures, particularly those with hypospermatogenesis, for whom sperm could be retrieved via a single TESE without prior repair.

In summary, although some evidence suggests potential benefits of varicocelectomy in men with NOA, the current literature lacks sufficient quality to support a strong recommendation for this procedure in those with a varicocele. At present, the panel can only advise on the possible benefit of surgical correction restricted to clinically detectable varicocele in NOA patients without known genetic abnormalities and with a partner who has no evidence of diminished ovarian reserve. Patient counseling should highlight the variability of the outcome data and the limited strength of existing evidence. There is a need for high-quality prospective studies, ideally including genotyped cohorts, to clarify the benefit of varicocelectomy in NOA.

Conflicts of interest: The authors have nothing to disclose.

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