Editorial

Can we reliably predict sperm recovery in semen of nonobstructive azoospermia men after varicocele repair?—answers are awaited

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Nonobstructive azoospermia (NOA) refers to repeated inability to detect sperm in the centrifuged pellet of semen due to primary testicular failure (1,2). NOA is not uncommon, affecting approximately 1% of all men and 10% of infertile men (3). Clinical varicocele has been implicated as a main cause of testicular dysfunction and infertility in 4.3% to 13.3% of NOA men (4-6). The widespread adoption of in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) during the last three decades has driven more interest in varicocele repair (VR) among men with NOA and clinical varicocele. VR in NOA men has been claimed to restore spermatogenesis, induce sperm recovery in ejaculate, improve testicular sperm retrieval rates (SRRs), decrease sperm DNA fragmentation and improve pregnancy rates. Nevertheless, restoration of spermatogenesis after VR is inconsistent and the reported rates of sperm recovery are variable, ranging from 0% to 57% (4,7,8). Noteworthy, the current literature lacks reliable predictors of successful sperm recovery in ejaculate after VR. Several clinical predictors—such as age, duration of infertility, testicular volume, grade of varicocele, laterality of varicocele and serum levels of testosterone, LH, FSH and estradiol—have been studied and shown to be undependable (7-12). In contrast, testicular histology has been reported as a strong predictor of sperm recovery (3,7). Thus, identifying other more reliable prognostic factors is still welcomed. Notably, identifying gene expressions and molecular pathways involved specifically in the pathophysiology of NOA with varicocele might help predicting the outcome of VR.

In a recently published report in the *Journal of Urology* (13), Shiraishi and his group from Japan have examined a cohort of 83 men with a mean age of 34.8 years, NOA and clinically palpable left varicocele to determine the predictors of successful sperm recovery in semen within 1 year after VR. They excluded patients with cryptorchidism or known genetic abnormalities. All patients had undergone simultaneous left sided microsurgical inguinal VR and bilateral testicular biopsies. The investigators used testicular histological patterns, genome-wide whole mRNA expression analysis (transcriptome) of testicular tissues and the number of proliferating nuclear cell antigen (PCNA) positive cells in testicular samples with maturation arrest (MA), as well as other clinical and laboratory criteria, to assess for prediction of sperm recovery after VR.

In their report, 24% of patients have recovered sperm in ejaculate within 1 year, with statistically significant differences between sperm recovery rates among various histological patterns [2%, 37% and 69% in Sertoli-cell only (SCO), MA and hypospermatogenesis (HS), respectively]. Fifty three men failing to demonstrate sperm recovery after VR had undergone micro-TESE with a mean SRR of 36%. Similarly, significant SRRs differences were noted between the SCO, MA and HS patterns (20%, 57% and 100%, respectively). Transcriptome analysis screening 23,003 genes was performed to identify the 20 top-ranked genes that were differentially up-regulated or down-regulated in the testicular tissue of men with MA with or without

sperm recovery after VR. The testes that responded to VR with sperm recovery have shown differentially up-regulation of cell cycle related genes (including CYLC2, BRCA1, CYLC1 and PCNA) and down-regulation of genes coding for antioxidants (including SOD1, CAT and GSTA4). To further assess the role of cell cycle related genes, immunohistochemical testing for PCNA molecular expression was done along with counting the PCNA positive cells in testicular tissues of MA patients. The number of PCNA positive cells was significantly higher in men exhibiting sperm recovery compared to those with no sperm recovery. PCNA expression was the only independent prognosticator that significantly correlated with sperm recovery in the ejaculate after VR, while none of other clinical parameters or biomarkers demonstrated significant correlation with sperm recovery.

Shiraishi and co-authors should be commended for their study. The study has confirmed that VR could induce sperm recovery in ejaculate of 24% of men with NOA. Transcriptome analysis and immunohistochemistry for PCNA are important step-forward to predict sperm recovery. However, there are several concerns, questions and limitations that undermine the level of evidence provided by the study and might seriously affect the validity and applicability of the findings:

(I) The authors did not explicitly describe the study type (prospective, retrospective, etc.);

(II) The most critical shortcoming of this study is the lack of a control group undergoing no VR but receiving the same diagnostic and follow up procedures. The last concern is particularly important when assessing the validity of the study findings of sperm recovery rates and SRRs after VR. In fact, "Should we defer micro-TESE to a later time after VR to improve the SRR in men with NOA?" is a compelling question in practice. A properly conducted controlled trial is indispensable to help answering such question;

(III) Only patients with left sided varicocele were included in the study. Since many of NOA men have bilateral varicoceles, the study findings should be cautiously applied to the population with bilateral disease;

(IV) Transcriptome analysis and immunohistochemical tests for PCNA were done on testicular samples, which may or may not represent the actual predominant histological pattern;

(V) Transcriptome analysis and immunohistochemical tests for PCNA were reported in MA only, thus these findings may not apply to NOA men with other histological patterns;

(VI) In men with early MA, the authors observed surprisingly high sperm recovery rate (20%) and SRR (40%), which are not in-line with the previously reported literature (7,8);

(VII) The authors studied the predictors of sperm recovery in semen within 1 year after VR. Since a good number of patients (53 patients) underwent micro-TESE after VR with a 36% SRR, I wish the authors could report the predictors of successful testicular sperm retrieval as well.

In our experience (unpublished data), some clinical criteria can help predict successful sperm recovery and sperm retrieval in micro-TESE. We have observed that improvement of serum testosterone levels after repair of varicocele can predict improvement of semen quality in infertile men with hypogonadism. In fact, some NOA patients are virtually azoospermics who swing between "absent" sperm and appearance of "few thousands" sperm insufficient for ICSI. Other men may intermittently demonstrate "occasional" sperm in their ejaculate. Those patients usually fare better than patients demonstrating "persistent" azoospermia and have higher chances of ejaculate sperm recovery and better SRR if they ultimately need micro-TESE. We have also observed that men with secondary infertility or documented previous positive sperm retrieval do better. Nevertheless, our observations are anecdotal and require robust randomized clinical trials to examine their legitimacy.

The strongest predictors of sperm recovery, in Shiraishi *et al*. study and in other studies (7,13), still rely on testicular tissue sampling. Since testicular biopsies are mostly taken concurrently at time of VR, we are able to predict the outcome of repair only after performing the repair. Therefore, we should strive for finding out less invasive prospective predictors to precede VR or micro-TESE; optimistically genetic or molecular analysis of peripheral blood or seminal fluid. In real world, one of the most challenging patients' questions is "are there any factors that might help predicting sperm recovery in my semen after VR"? The question is still open; answers are awaited.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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