Re: Evaluation of Microdissection Testicular Sperm Extraction Results in Patients with Non-Obstructive Azoospermia: Independent Predictive Factors and Best Cutoff Values for Sperm Retrieval

The authors from Turkey smartly show the predictive factors for successful sperm retrieval rate (SRR) with microdissection testicular sperm extraction (micro-TESE), carried out on men with non-obstructive azoospermia (NOA). In men with NOA, retrieval of spermatozoa provides a chance for fatherhood, in spite of very scares sperm production. Men go through assessment for infertility are found to have azoospermia in their ejaculate in up to 10% of the cases.[1] Around 60% of these cases are due to NOA.[2] Men with NOA need some type of sperm retrieval (SR) technique in combination with intra-cytoplasmic sperm injection (ICSI) to have their own children. There are some methods for SR, including, percutaneous testicular biopsy, fine needle aspiration (FNA), open testicular biopsy (testicular sperm extraction (TESE), which includes multiple TESE), and micro-TESE. Micro-TESE is now one of the most popular SR techniques for men with NOA. Although the success of micro-TESE compared to other SR techniques has been widely documented, a complete judgment of predicting preoperatively whom the technique is going to be successful is not totally clear and remains controversial. In addition reported SRR can be biased either by including patients demonstrating nearly normal spermatogenesis, or by inclusion of patients without available testicular histology. Therefore, successful SRRs reported in the literature for NOA men differ from around 30% to level more than 80%. In well-designed studies with well-defined men with NOA, the reported successful SRRs after a first TESE attempt is about 50%. Nonetheless, due to invasive nature of TESE, men with NOA want to have a well prediction of likelihoods of successful SRR than tossing a coin. Since testicular volume and serum follicle stimulation hormone (FSH) levels are routinely evaluated in men with azoospermia, these parameters are regularly used, alone or in combination, to predict successful SR. Unfortunately, their predictive value remains restricted and is subject to the demographic and clinical characteristics of the studied patients with NOA. Idem ditto for the predictive parameters for successful SR has been published by Boitrelle and colleagues.[3] The positive likelihood ratios for the stand-alone parameters are less than 2 and hereafter not of a great diagnostic power in predicting testicular SRR. With a positive likelihood ratio of 3, a predictive score combining serum FSH concentration, testicular volume, and serum inhibin-B level, seems more favorable in their setting. Nevertheless again, is this a strong predictive model appropriate to every men with NOA? All seminiferous tubules (ST) must be inspected to recognize small foci of normal spermatogenesis. The STs are extremely coiled within very fine septae. The dissection should be performed between tubules to permit access to deeper portions of the STs. The space between the tubules and the tunica is very vascular, thus hemorrhage that would be very difficult to control can happen if dissection is made in this plane. To avoid separation of STs from their blood supply and thus devascularization of the STs, unnecessary force during the dissection should be avoided. Postoperative hemorrhage and hematoma formation after micro-TESE can result in scar formation within the testis. Cautious dissection and careful hemostasis, will minimize these complications. Microdissection continues until sperm are found or all areas of both testes are examined. Usually, small samples of 2-10 mg are taken. If sperm are not found in one testis, the process should be repeated in the contralateral testis. When sufficient sperm are obtained, hemostasis is accomplished using bipolar cautery.

Improvement of spermatogenesis before proceeding to SR should be tried in cases where the female age permits. Hormonal therapy can increase endogenous testosterone (T) production and normalize the testosterone/estrogen ratio in men with documented hypogonadism. Hormonal therapy includes administration of aromatase inhibitors, clomiphene citrate, and human chorionic gonadotropin (HCG). In patients with Klinefelter's Syndrome and low serum T level, when T increases to greater than 250 ng/dL with medical therapy, SRR with micro-TESE will be higher.[4] The rationale behind of such treatment based on the fact that most men with NOA have small testes with reduced T production and hypogonadism. Sufficient intratesticular androgen levels are vital to maintain normal spermatogenesis. In some cases with NOA gonadotropins administration are worthwhile, these include

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men with NOA and testicular histology demonstrating hypospermatogenesis, and men who had failed initial micro-TESE.[5] Men with NOA may benefit from clomiphene citrate administration even with serum normal T level.

Up till now, there are yet no absolute preoperative predictive criteria for successful SR in men with NOA. FSH, serum T levels and testes volume indicate global testicular function and are not indicator for presence of a site of normal spermatogenesis within a testis. Despite the widespread use of TESE, consistent clinical and laboratory prognostic factors of SR are lacking. In the literature there are many proposed prognostic factors including testis size, serum FSH, inhibin β, genetic alterations and the etiology of infertility; nevertheless, the histological testicular pattern remains the best predictor of SR, although with the awkwardness of a second invasive procedure. Testicular histopathology examinations, in contrast, provide better prognostic factor compared with the aforementioned markers. SRRs by micro-TESE are considerably higher in hypospermatogenesis (93%) compared with maturation arrest (64%) and sertoli cell only syndrome (20%).[6] The best method to identify sperm-containing ST is using from operating microscope. The best sensitivity and specificity for a positive result on SR is achieved with 250 μ slices. Currently we need a novel techniques which can help us in the detection of sperm-producing ST without the necessity of tissue removal. Multiphoton microscopy has been used successfully to differentiate normal from abnormal spermatogenesis both in animal model and in humans.[7,8] Confocal fluorescence microscopy has also been applied in a murine model of micro-TESE.[9] In addition, full field optical coherence tomography, is a useful tool to simplify real-time visualization of spermatogenesis in an ex vivo rodent SCO model.[10]

There is no individual characteristic or factor that can absolutely predict the ability to SR during a surgical procedure. While preoperative factors still do not offer an accurate model to predict success of micro-TESE, data on literature demonstrate that a combination of these factors can be used to counsel patients and help guide clinical decisions.

Testicular SR is a feasible and successful procedure. Testicular spermatozoa can be retrieved from the testis even in men with testicular azoospermia and severe impaired spermatogenesis. But, surgical injury of the testis might also damage the interstitial compartment of the testis with testosterone deficiency as a result. Therefore, endocrine follow-up is mandatory following micro-TESE.

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Microdissection testicular sperm extraction (micro-TESE) is the most popular and acceptable method for sperm retrieval (SR) according to our knowledge. Yes we agree with you, the success rate of SR were found between 30% and 80% in several studies and also success rate in SR varies depending on the degree of disorder in testicular pathology. The most important thing is that to what percentage of the sperm found and which histologic subgroup. Therefore, it's more proper that we consider success rate into each subgroup instead of total success rate. If we have all patients with hypospermatogenesis, of course we will have high success rate, in contrast if we have done micro-TESE in patients with just sertoli cell only syndrome we will have low success rate. In addition as you mentioned the success rate is around 50% in patients with non-obstructive azoospermia (NOA) in well-defined studies. I would like to mention again Azoospermia factor (AZF) deletion should be evaluated in patients with NOA in additional to routine parameters which you recommend. Because, AZF deletion were more common in patients with azoospermia and oligozoospermia and also AZF deletions have diagnostic and predictive values. Evaluation of Y chromosome microdeletions in NAO were strongly recommended by guidelines. In case of complete microdeletion of AZFa or AZFb micro-TESE is not necessary due to unlikely sperm found.[1] Urologist should avoid extreme dissection which can cause scar to preventimpaired testosterone production. We agree with what you said about hormone therapy.

Janosek-Albright and colleagues reported that medical treatment was effective and recommended for men with hypogonadotropic hypogonadism; therefore, medical treatment can often obviate the need for sperm retrieval techniques.[2] The aim of hormonal manipulation was to increasing endogenous production of testosterone and normalizing the testosterone/estrogen ratio in men with clear hypogonadism. Men with hypospermatogenesis, men who failed initial micro-TESE but before a repeat micro-TESE, might benefit from a trial of gonadotropins.[2]

Certainly, there were not predictive factors which clinically clarified. As you mentioned above the best predictive factor is testicular histology. We also would like to mention that, the fiberoptic confocal microscopic study on animalresults inhigher SR success rate and lower operation time.

Everaert and colleagues evaluated the effect of micro-TESE on androgens in long term follow up and they found that de novo androgen deficiency occurred in 16% of the male patients following micro-TESE, indicating that, in men with NOA, long term hormonal follow up is recommended after micro-TESE.Long-term androgen deficiency is a potential risk of micro-TESE and patients with NOA need to be informed about this possible complication.[3]

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