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PREDICTIVE FACTORS OF SUCCESSFUL MICRO-DISSECTION TESTICULAR SPERM EXTRACTION IN NON-OBSTRUCTIVE AZOOSPERMIA

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Abstract

The absence of spermatozoa in semen analysis is a sign of non-obstructive azoospermia (NOA), which is caused by either inadequate or nonexistent generation of fully mature spermatozoa inside the testicles. For individuals with non-obstructive azoospermia, testicular microdissection (TESE) is acknowledged as a safe and successful technique, irrespective of the many underlying causes and preoperative assessments. Hormone levels, age, and the size of the testicles are not reliable markers of the success of a micro-TESE**.** In males with NOA, especially those who have had several failed biopsies, successful sperm retrieval through microdissection TESE is frequently achievable. Additionally, diagnostic biopsy can provide valuable insights into the likelihood of obtaining sperm during the microdissection TESE procedure.

Keywords: Azoospermia, sperm retrieval, Micro-TESE, and male infertility

Introduction

One in six couples experience infertility, with male factor infertility accounting for half of these occurrences. The most severe type of male factor infertility is azologlossia, or the total lack of spermatozoa in the ejaculate. This condition is classified as both obstructive and non-obstructive azoospermia (NOA and OA). NOA arises from a disruption in spermatogenesis, while OA is the result of blockages within the testicular and genital ductal systems. It is estimated that NOA affects approximately one in every 100 men [1].

At the moment, the most advanced surgical technique for extracting sperm from the testis is thought to be microsurgical testicular sperm extraction, or micro-TESE. This method uses powerful microscopes to precisely identify the white tissue that may contain sperm. Micro-TESE has demonstrated sperm retrieval rates (SRRs) ranging from 30% to 70%, demonstrating its effectiveness in sperm extraction from patients with non-ocular oxygen deficit. The factors that positively indicate successful sperm retrieval and the overall outcomes of micro-TESE in NOA patients are yet unknown, nevertheless.

It has been suggested that variables like age, testicular size, and pretreatment hormone levels might be used to predict the outcome of micro-TESEs [2].

Azoospermia

The total absence of spermatozoa in two distinct centrifuged semen samples is what is referred to as azoospermia, whereas the absence of ejaculation is the definition of aspermia. This disorder is seen in 10% to 15% of male infertile cases and affects roughly 1% of the male population overall.

Various untreatable testicular disorders can lead to azoospermia, which is considered the most severe type of male infertility [3]. Azolospermia is the absence of spermatozoa in two different semen samples, whereas aspermia indicates the total absence of ejaculation. This condition affects 1% of all males and 10% to 15% of infertile men. There are three types of reasons for azoospermia: pre-testicular, testicular, and post-testicular. The classification of azoospermia as obstructive or nonobstructive is contingent upon the existence of obstructions in the ductus or vas deferens [4].

Nonobstructive Azoospermia

Patients with Nonobstructive Azoospermia (NOA) may present with normal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), although elevated levels are frequently observed. Testicular size can vary, being classified as normal, hypotrophic, or atrophic. In instances where the diagnosis remains ambiguous, a testicular biopsy may be necessary [5].

- **Evaluation of Nonobstructive Azoospermia**

At least two distinct semen samples must be analyzed to diagnose azoospermia. An aberrant hormonal profile in the setting of NOA usually signifies a substantial spermatogenic abnormality, which is frequently shown by an increased FSH level. In cases when the hormonal profile is normal, spermatogenesis can be further investigated using a testicular biopsy, this is the gold standard for distinguishing Sertoli cell-only disease and maturational arrest from azoospermia.

To find any genetic anomalies, Y chromosome microdeletion testing, genetic testing, and karyotype analysis should also be carried out. Endocrinological problems must be correctly identified and treated [6].

- **Management of Nonobstructive Azoospermia**

1) **Testicular Fine Needle Aspiration (TFNA):** 1) Testicular Fine Needle Aspiration (TFNA): This minimally invasive method is utilized to retrieve sperm when azoospermia is not obstructive. This technique entails aspirating testicular tissue with a tiny needle and checking it for sperm. Comparing the process to other surgical methods, it is less invasive since it is simpler and may be done under local anesthesia [7].
2) **Percutaneous Testicular Sperm Extraction (PTSE)** is a technique designed to obtain sperm from the testicular tissue using a larger gauge needle compared to TFNA. This method involves aspirating testicular tissue through a needle, which is connected to a syringe [8].
3) **Percutaneous Epididymis Sperm Aspiration (PESA)** is a method that is usually used to retrieve sperm from cases of obstructive azoospermia, while it can also be employed in some non-obstructive cases [9].
4) **Microsurgical Epididymis Sperm Aspiration (MESA)** is an advanced variation of the traditional epididymal sperm aspiration techniques, designed to optimize sperm retrieval from the epididymis using microsurgical techniques [10].
5) **Micro-dissection Testicular Sperm Extraction (micro-TESE)**

The micro-sectioning method When sperm is needed for severe non-obstructive azoospermia, a sophisticated and highly specialized process called testicular sperm extraction (micro-TESE) is used. This method accurately divides seminiferous tubules that are capable of producing sperm under a microscope. To look for active sperm production sites in the testicular parenchyma under high magnification, a larger incision is performed in the tunica albuginea [11].

The primary advantage of micro-TESE is its ability to maximize the chances of retrieving viable sperm by targeting specific areas within the testis where sperm production is more likely. For individuals with severe types of non-obstructive azoospermia, this accuracy makes sperm retrieval more likely to be effective and minimises the need for numerous treatments. Furthermore, testicular devascularization and haematoma development can be less common when microsurgical procedures are used since there is less chance of harm to the testicular blood supply [12].

Predictors of Microdissection TESE Success

Minuscule dissection TESE is frequently performed in tandem with an IVF cycle that is scheduled. For infertile couples, microdissection TESE-IVF/ICSI cycles can be emotionally and financially taxing, yet concurrent sperm retrieval and IVF seem to yield the best treatment outcomes. It's critical to talk about reasonable expectations for the results of reproduction [13].

- **Effect of Prior Biopsy or Conventional TESE Procedure**

It has been demonstrated that microdissection TESE helps men with non-obstructive azoospermia (NOA) successfully retrieve sperm, even in cases where multiple previous biopsies have yielded negative results. Research indicates that approximately 50% of these patients needed to undergo several biopsies, with the number ranging from 2 to 14, to successfully obtain sperm. At Weill Cornell, researchers looked at how conventional TESE and prior negative biopsies affected the microdissection TESE sperm retrieval rates in males with NOA.

The findings revealed that the success rate for sperm retrieval in individuals who had not undergone any prior biopsies was 56%, this was significantly more than those who underwent one to two biopsies per testis (51%) or three to four biopsies per testis (23%; $p = 0.04$). On the other hand, following a successful sperm retrieval, repeat microdissection TESE showed a success rate ranging from 60% to 80%. However, in instances where sperm were not identified during a previous microdissection TESE, the sperm retrieval rate significantly decreased to 33% [14].

- **Testicular Histology on Diagnostic Biopsy**

When predicting the chance of a successful sperm retrieval during a microdissection TESE technique, diagnostic biopsy is a useful tool. It is important to note that this type of biopsy does not encompass all regions of the testis, which may result in the oversight of small areas exhibiting more advanced pathological patterns. Nevertheless, four distinct testicular histologies are recognized in the context of non-obstructive azoospermia (NOA). The least severe variation of NOA, hypospermatogenesis, has the greatest surgical sperm retrieval rate (SRR), ranging from 73% to 100%. On the other hand, the SRR for early maturation arrest is 27% to 40%, late maturation arrest is 27% to 86%, and the SRR for Sertoli cell-only syndrome (SCOS), the most severe kind of infertility, is 22.5% to 41%.

The insights gained from a diagnostic biopsy may carry significant implications for patient counseling. Notably, the presence of heterogeneity within the testis emerges as a critical factor in

predicting sperm retrieval in cases of NOA. Since all males with NOA have aberrant spermatogenesis, finding a distinct or more developed spermatogenic pattern might be a sign of sperm retrieval, especially in those who mostly show Sertoli cell-only results on biopsy [14].

The histopathological patterns were assessed using the Modified Johnson scoring system, which assigns a score ranging from 1 to 10 based on the evaluation of testicular biopsies. The scoring criteria are as follows: - Score 10: Complete spermatogenesis [14].

- Score 10: Complete spermatogenesis

- Score 9: Incomplete spermatogenesis with numerous late spermatids

- Score 8: Fewer than 5 spermatozoa per tubule and a limited number of late spermatids

- Score 7: Numerous early spermatids present, but no spermatozoa or late spermatids

- Score 6: A small number of early spermatids, with no spermatozoa or late spermatids

- Score 5: Many spermatocytes present, but no spermatozoa or spermatids

- Score 4: Few spermatocytes present, with no spermatozoa or spermatids

- Score 3: Only spermatogonia are present

- Score 2: Presence of Sertoli cells only, with no germinal epithelial cells

- Score 1: Absence of seminifer

- **Microdissection TESE in Setting of Elevated FSH Levels**

Sertoli cells' inhibin production decreases in testicular failure. The decrease in negative feedback leads to an increase in FSH synthesis in the anterior pituitary. High FSH levels indicate impaired spermatogenesis. FSH levels, however, are not a very good indicator of whether testicular sperm extraction (TESE) would be successful after microdissection. The most advantageous regions of spermatogenesis—which are not indicated by serum FSH levels—are what ultimately influence the possibility of successful sperm retrieval, even if serum FSH can indirectly reveal the general histological state of the testes [15].

To test the theory, a total of 800 males with NOA underwent microdissection TESE, and the results were analyzed. Based on their blood FSH levels, the subjects were divided into four groups: less than 15, 15 to 30, 31 to 45, and higher than 45 IU/mL.

The influence of FSH levels on sperm retrieval rates was found to be limited. Specifically, an FSH level below 15 IU/mL was linked to a 51% reduction in response rates, while levels between 15 and 30 IU/mL were associated with a 60% decrease in response. The sperm retrieval rates for FSH levels of 31 to 45 IU/mL and above 45 IU/mL were recorded at 67% and 60%, respectively. Notably, patients with FSH levels exceeding 90 IU/mL demonstrated consistent sperm retrieval rates. It was determined that the effectiveness of sperm retrieval after microdissection is not dependent on FSH levels. Moreover, individuals with azoospermia and normal FSH levels can constitute a different kind of infertility. Poor sperm retrieval results were seen in some individuals

with diffuse maturation arrest, even if they had normal FSH levels and sufficient testicular volume [16].

- **AZF Deletions**

70% of men with AZFc deletions, though typically at low concentrations below 1 million per milliliter, are capable of having sperm present in their ejaculate, making their probability of achieving reproduction success comparable or considerably greater than that of typical NOA patients, with a 60–70% reported success rate. The DAZ gene's AZFa, AZFb, or AZFc regions include Y chromosomal microdeletions in 6–18% of males with NOA or severe oligozoospermia.

Isolated AZFc deletions have a comparable or even higher probability of producing sperm in the testis compared to other NOA patients. Sperm can be found in ejaculate in 70% of males with AZFc deletions, but only in trace amounts—typically less than 1 million per millilitre. Of azoospermic males with AZFc deletions, 60–70% are able to reproduce [17, 18].

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