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REVIEW

Surgical management of nonobstructive azoospermia

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Abstract Nonobstructive azoospermia (NOA) is characterized by the complete absence of sperm in the ejaculate due to testicular failure. The evaluation and management of patients with NOA offer a challenge to the reproductive urologist. In the era of *in vitro* fertilization with intracytoplasmic sperm injection, surgical sperm extraction techniques can afford men with NOA biologic paternity. To provide a comprehensive review of surgical sperm retrieval approaches in the patient with NOA emphasizing complications, success rates and outcome optimization, a Medline search was conducted querying surgical approaches used to manage NOA. Four sperm extraction techniques are described including: testicular sperm aspiration, testicular sperm extraction, fine needle aspiration mapping and microdissection testicular sperm extraction. In addition, the roles for pre-extraction varicocelectomy and sperm cryopreservation are discussed. The management of NOA continues to evolve as newer tools become available. Several modalities of sperm acquisition exist. An understanding of their complications and success rates is fundamental to the treatment of NOA.

1. Introduction

Azoospermia is characterized by the complete absence of sperm in the ejaculate, affecting up to 15% of men seeking an infertility evaluation. Approximately 60% of cases of azoospermia are caused by primary or secondary hypogonadism, termed nonobstructive azoospermia (NOA) [1]. Possible etiologies span a spectrum including genetic disorders or local testicular insults [2,3] that result in impaired

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spermatogenesis or disruption of the hypothalamic-pituitary-testis (HPT) axis. The conditions leading to NOA represent some of the most challenging of infertility management.

Although the underlying cause of NOA may be occasionally correctable (i.e., hypogonadotrophic hypogonadism), most of these patients will require advanced reproductive technologies. With the introduction of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in the 1990s, many of these men can now father their own biologic children. IVF-ICSI combined with sperm extraction techniques are now considered standard practice and are conducted routinely worldwide.

For successful IVF-ICSI only a few viable sperm are required. In those patients with NOA, even very low levels of spermatogenesis can be exploited with surgical sperm extraction. Several techniques to retrieve sperm from the testes have been described, each with a unique set of advantages and disadvantages. In this review we summarize the surgical management of NOA and seek to clarify the implications of each approach.

2. Initial evaluation

A diagnosis of azoospermia is made after two separate semen analyses demonstrate the lack of spermatozoa in centrifuged specimens. An interval of at least 3 weeks should be allowed to pass between samples. It is important to rule out possible collection error or retrograde ejaculation when interpreting samples with low volumes (less than 1.5 mL). Once azoospermia is confirmed, one must differentiate between obstructive or nonobstructive etiologies.

A thorough history and physical examination provide the basis for further testing. A focused history investigates the inherent endocrine and exocrine function of the testes. Symptoms consistent with low testosterone may represent deficiencies in androgen production, often found in conjunction with NOA. A prior history of paternity should not be considered specific to either form of azoospermia. The clinician should also inquire about risk factors that may help guide further evaluation (Table 1).

Table 1 Risk factors for azoospermia.

Type of azaspermian	Risk factors
Nonobstructive azoospermia	Cryptorchidism Delayed puberty Chemotherapy or radiation Testosterone replacement therapy Anabolic steroid abuse History of orchitis (mumps) Toxin exposure (heavy metals, pesticides)
Obstructive azoospermia	Prior scrotal surgeries Inguinal hernia repair Recurrent respiratory tract infection (cystic fibrosis, Young syndrome) Pelvic/scrotal trauma Reproductive malformation (prostatic cyst, absence of the vasa deferentia) History of epididymitis History of prostatitis

A detailed physical exam will often secure the diagnosis. The general exam can be useful in detecting stigmata of an endocrinopathy or genetic abnormality with particular awareness to gynecomastia and signs of impaired virilization. Careful attention should be paid to the scrotal exam. Surgical scars in the scrotum and inguinal region may provide evidence for prior surgery. Palpation of the spermatic cord allows the identification of possible varicoceles and to ensure the presence of both vasa deferentia. Decreased testicular volumes (below 15 mL) substantially raise suspicion for NOA. Finally, a digital rectal examination can be helpful in palpating obstructing midline cysts or fullness of the seminal vesicles.

Initial laboratory testing includes morning serum testosterone and follicle stimulating hormone (FSH) levels to help delineate the health of the Leydig and Sertoli cells, respectively. An FSH level above 7.6 mIU/mL supports an NOA diagnosis [4]. Any abnormalities on initial screening should prompt a full evaluation of the HPT axis. Classically, NOA patients will have normal volume, normal pH, azoospermic semen analyses with small-volume testes and an elevated FSH. Karyotype and Y chromosome microdeletion testing should be obtained in any patient with suspected NOA as chromosomal abnormalities are common in this population [5].

3. Evidence acquisition

A Medline search was conducted using the following search terms: nonobstructive azoospermia, sperm retrieval, testicular sperm extraction, fine needle aspiration, fine-needle mapping, testicular sperm aspiration, microdissection testicular sperm extraction, and cryopreservation. This search aimed to identify randomized, observational and descriptive studies describing the surgical management of NOA patients. As no randomized trials were available, observational and descriptive studies are discussed in this review.

A total of four techniques were commonly addressed and are described below, including testicular sperm aspiration (TESA), traditional testicular sperm extraction (TESE), fine needle aspiration (FNA) mapping, and microdissection testicular sperm extraction (microTESE). Two adjunctive procedures — cryopreservation and the role of varicocelectomy — are also discussed in the context of NOA management.

4. Evidence synthesis

4.1. TESA

Testicular sperm can be retrieved via percutaneous aspiration of testicular tissue. This technique was initially described for diagnostic purposes before it was adapted as a therapeutic approach [6]. The sample is acquired by aspirating through a fine (22-gauge) or large bore (18-