Reproductive Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Reproductive Biology

journal homepage: www.elsevier.com/locate/repbio

# Successful microdissection testicular sperm extraction for men with non-obstructive azoospermia

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ARTICLE INFO

*Keywords:*
Microdissection testicular sperm extraction
MD-TESE
Azoospermia
Male infertility
NOA

ABSTRACT

Non-obstructive azoospermia (NOA) is the most severe form of male infertility, defined by lack of spermatozoa in the ejaculate caused by impaired spermatogenesis. The chance of biological fatherhood of these men has been improved since the introduction of microdissection testicular sperm extraction (MD-TESE) combined with intracytoplasmic sperm injection. A thorough patient evaluation preoperatively is essential to recognize any underlying conditions, and to assist in patient counseling on the sperm recovery rate and pregnancy results. This review article summarizes the present data on MD-TESE to reach optimal results is treating men with NOA.

## 1. Introduction

Infertility is a common condition affecting nearly 20% of the couples wishing to conceive. At least mild male factor is thought to be present in about half of the infertility. The most severe form of male infertility is azoospermia, the complete lack of spermatozoa in repeated semen analyses. The prevalence of azoospermia is estimated to be 1% of all males [1] and 10–15% of infertile men [2]. In obstructive azoospermia (OA), the spermatogenesis in the testis is normal but due to blockage of the genital tract no spermatozoa are found in semen. In contrast, in non-obstructive azoospermia (NOA), the spermatogenetic function of the testis is severely impaired.

Intracytoplasmic sperm injection (ICSI) has revolutionized the treatment of male infertility, enabling fertilization of oocytes with very small numbers of spermatozoa. Biological fatherhood has been possible for men with OA since the early 1990s through epididymal or testicular sperm needle extraction or aspiration biopsies [3]. In men with NOA, however, sperm recovery is difficult with these techniques, since the spermatogenesis in NOA is only present in small areas, if any [4]. However, in microdissection testicular sperm extraction (MD-TESE), these areas are visualized using an operating microscope, giving a realistic sperm recovery rate of 40–60% [5].

The aim of this review article is to discuss the data available on MD-TESE, giving practical advice on how to reach the best possible results in MD-TESE to enable the chance of biological fatherhood for men with NOA. We also assess the current pregnancy outcome results following MD-TESE-ICSI. The importance of patient counseling prior to the decision of surgical sperm recovery trial cannot be overemphasized. This should be based all the relevant data on sperm recovery rate as well as chances for a pregnancy, including the evaluation of the potential fertility of the female partner.

## 2. Material and methods

### 2.1. NOA patient evaluation and preoperative preparation

The patient with azoospermia is evaluated with detailed medical and family history and a physical examination. The use of testicular ultrasound is recommended, since infertility is a risk factor for testicular neoplasm [6,7]. Hormonal evaluation should include serum follicle stimulating hormone (FSH), testosterone (T), luteinizing hormone (LH) inhibin-B levels, thyroid stimulating hormone (TSH), prolactin (PRL) and genetic testing should be performed to identify Klinefelter syndrome (KS) and Y chromosome microdeletions [8].

Identifying the men with NOA in a population of men with azoospermia can be done with good sensitivity and specificity [9]. Elevated serum FSH, small testicular size, certain genetic conditions, family history and medical history of cytotoxic medication, radiation or

*Abbreviations:* MD-TESE, microdissection testicular sperm extraction; TESE, testicular sperm extraction; TESA, testicular sperm aspiration; SRR, sperm recovery rate; ICSI, intracytoplasmic sperm injection; NOA, non-obstructive azoospermia; OA, obstructive azoospermia; hCG, human chorionic gonadotropin; TSH, thyroid stimulating hormone; CC, clomifen citrate; LBR, live birth rate; LH, luteinizing hormone; FSH, follicle stimulating hormone; T, testosterone; KS, Klinefelter syndrome; PVP, polyvinylpyrrolidone; SERM, selective estrogen receptor modulator

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https://doi.org/10.1016/j.repbio.2018.03.003
Received 29 January 2018; Received in revised form 16 March 2018; Accepted 17 March 2018

**Table 1**
Hormonal treatment options of male hypogonadism.

| Hormonal treatment | Dosage |
|---|---|
| Clomifen citrate (CC) | 25–50 mg daily perorally |
| Tamoxifen | 10–20 mg daily perorally |
| Anastrozole | 1–2 mg daily perorally |
| Letrozole | 2,5–5 mg daily perorally |
| Human chorionic gonadotropin (hCG) | 2500–5000 IU 2–3 times a week subcutaneously |
| Follicle stimulating hormone (FSH) | 75–150 IU 2–3 times a week subcutaneously |
| Human menopausal gonadotropin (hMG) | 75–150 IU 2–3 times a week subcutaneously |

cryptorchidism are valuable pieces of information to reach a reliable preoperative diagnosis.

### 2.2. Medical treatment

Nearly half of the men with NOA may present with some form of hypogonadism presenting as low serum T [11], and there is a consensus on attempting to reach normal serum T level prior to MD-TESE [12]. Exogenous testosterone administration suppresses the endogenous gonadotrophin levels and consequently depletes spermatogenesis in most men. Testosterone (as well as other anabolic steroids) is detrimental to spermatogenesis and should therefore be discontinued prior to MD-TESE [13]. Hormonal treatment of hypogonadism is aimed at normalizing the testicular T production and appropriate milieu for spermatogenesis (i.e. sufficient intratesticular T concentration). Treatment options include aromatase inhibitors (anastrozole, letrozole) and selective estrogen receptor modulators (SERMs, clomifen citrate or tamoxifen) [14] (Table 1). The diminishing of the estradiol feedback to the pituitary and hypothalamus causes an increase in gonadotrophin secretion. The appropriate hormonal response can be verified by the increase in serum LH and testosterone concentrations. If the T response is not sufficient, or the pituitary function is compromised, hCG treatment may provide favorable response in some men. Adverse effects seem to be mild, although the data is limited [15]. The potential beneficial and adverse effects should be recorded to adjust the medication (Fig. 1).

A patient subgroup that may potentially benefit from the testicular effect of aromatase inhibitors is men with Klinefelter syndrome (KS). The theoretical idea is to optimize testicular function and hormonal milieu for spermatogenesis through inhibiting elevated estradiol levels, this use of aromatase inhibitors may also further improve intratesticular T [16].

A fairly small proportion of men with NOA present with hypothalamic or pituitary impairment, leading to low circulating testosterone level and impaired spermatogenesis (hypogonadotropic hypogonadism). The appropriate treatment for these men is human chorionic gonadotrophin (hCG). The spermatogenesis may take up to 6–24 months to fully recover, and some men require additional recombinant FSH to obtain spermatogenesis [10].

### 2.3. Surgical retrieval of sperm in NOA

MD-TESE was introduced in 1999 [4], initially to reduce surgical complications of conventional TESE, especially by avoiding damage to the testicular vessels. The use of an operating microscope revealed the heterogeneous structure of the seminiferous tubules, allowing the selective biopsies of the most eligible tubules in terms of sperm production. The improvement in sperm recovery rate (SRR) was soon observed [4], and the method is now beginning to reach a gold standard status when treating men with NOA.

In OA, SRR of more than 90% is possible by testicular sperm aspiration (TESA) or epididymal sperm aspiration [17]. In NOA, needle

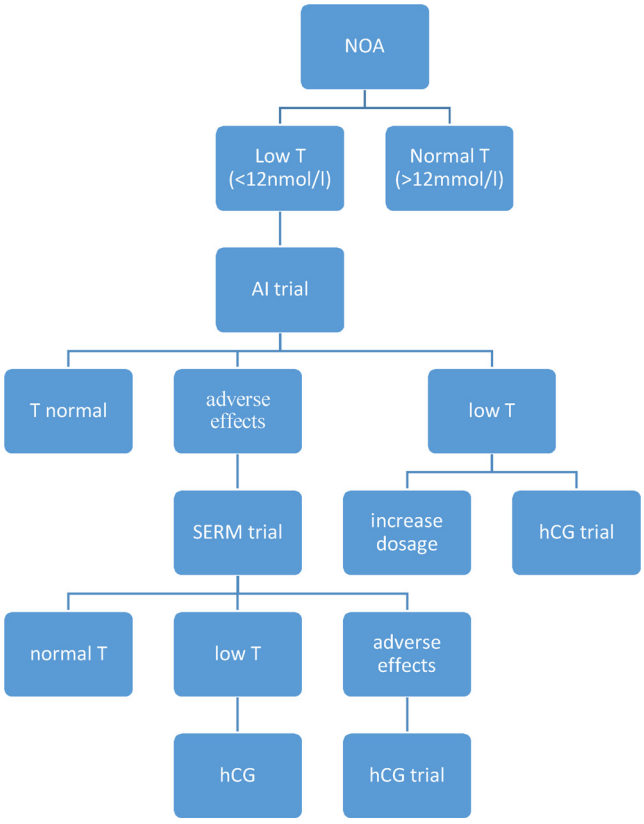


**Fig. 1.** Suggested flow chart for selecting the medication prior to microdissection testicular sperm extraction. NOA = non-obstructive azoospermia, T = serum Testosterone level, AI = aromatase inhibitor, SERM = selective estrogen receptor modulator, hCG = human chorionic gonadotrophin.

biopsy techniques are rarely successful, and mapping techniques have been introduced to reach higher success rates [18]. Larger gauge needles seem to increase SRR slightly [19], but the results are still inferior to MD-TESE. These techniques may serve to assist in predicting an individual patient's success rate, but rarely specifically enough to exclude men from MD-TESE.

According to a recent meta-analysis, MD-TESE is 1.5 times more effective in finding sperm compared to conventional TESE, while conventional TESE is still twice as likely to find sperm compared with TESA. The highest complication rates are associated with TESE while TESA is the cheapest method, when successful [20].

### 2.4. MD-TESE method

The MD-TESE literature is often criticized for inadequate description of surgical procedures involved, as well as the inconsistent reporting of the methods used in laboratory. Operating time is often not described, and the time used in laboratory also fails to be considered. There seems to be some learning curve involved with MD-TESE, for some presenting as improved SRR results and for others as reduced operating time [21,22].

#### 2.4.1. Surgical method of MD-TESE

MD-TESE can be performed under general anesthesia or in local anesthesia. Most western centers report the use of general anesthesia [23], while local anesthesia seems to be more popular in Asian centers [24]. Local anesthesia may be used to reduce post-operative pain in patients operated under general anesthesia.

The skin is incised in scrotal midline using a scalpel. The larger testis is chosen for incision through the tunica vaginalis with a monopolar instrument and the testis is lifted out of the scrotum. The tunica