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

Rauni Klami[a,*], Harri Mankonen[a], Antti Perheentupa[a,b]

[a] Department of Obstetrics and Gynecology, Turku University Hospital, Turku, Finland
[b] Institute of Biomedicine, Research Centre for Integrative Physiology and Pharmacology, University of Turku

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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

* Corresponding author at: Department of Obstetrics and Gynecology, Turku University Hospital, Turku, Finland.
E-mail address: rauni.klami@tyks.fi (R. Klami).

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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

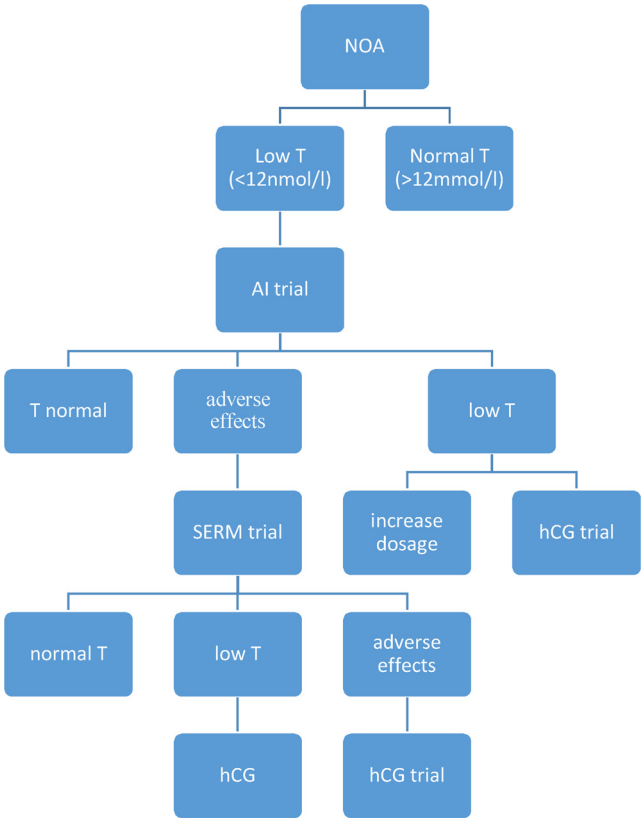

Fig. 1. Suggested flow chart for selecting the medication prior to microdissection testicular sperm extraction. NOA = non-obstructive azoospermia, T = serum Testosterone level, AI = aromatase inhibitor, SERM = selective estrogen receptor modulator, hCG = human chorionic gonadotrophin.

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

albuginea is then incised with scalpel under an operating microscope. A transverse incision is sometimes recommended to avoid the equatorial vessels, but we as well as many others also report vertical incision with no increase in complication rates. In our experience, the vertical incision typically reveals more testicular tissue for analysis. Furthermore, once the tissue has been evaluated and biopsied, the closure of a vertical incision is easier. Mosquito clamps are placed on both sides of the tunical incision. The surgeon or the assisting surgeon will be able to adjust the focus and help to gain visualization of the most opaque and dilated seminiferous tubules by gently exposing and moving the tissue with the mosquito clamps. With an operating microscope at 20-fold magnification, the tubules are systematically examined to target the biopsies at the most potential loci for spermatogenesis. Microsurgical forceps and scissors are used to remove the tubules for biopsies, which are placed in a cell culture plate containing sperm transport buffer and are immediately examined by higher magnification (the method described in next paragraph). If no sperm is recovered, operating on the first testis is discontinued after the entire testis has been examined. Hemostasis is ensured using bipolar electrocauterization, the tunica albuginea is closed in running suture using 5-0 monofilament suture. The testis is then placed back in the scrotum, the tunica vaginalis is closed using 5-0 monofilament suture and the contralateral testis is operated on in the same manner, if necessary. The skin is closed with 4-0 absorbable suture in running intracutaneous fashion. Infiltrating local anesthetic after the procedure will reduce the need for post-operative pain medication and is therefore recommended (1% lidocaine + 0.75% bupivacaine, 10 ml for each side).

2.4.2. Laboratory procedures in MD-TESE

The individual biopsies are transferred to one well dishes in 0.5 ml of equilibrated cell culture media. Five to ten biopsies are quickly screened through after a rapid dispersion to inform the surgeon whether sperm cells can be identified. If no sperm cells are seen, the embryologist mechanically disperses the tissue by squeezing out the intratubular cell mass using fine needles (e.g. 27 g) to produce a suspension. Larger cell clusters can be dispersed by aspirating cell clusters carefully up and down in a 23 g needle. This procedure is necessary especially in spermatogenic arrest samples due to the large amount of intratubular cell mass. Some prefer a collagen digestion to disperse the remaining cell clusters [25]. Our experience from the first 100 operations showed no benefit from collagen digestion after unsuccessful manual dispersion. Since no additional spermatozoa were obtained after the digestion, we discontinued the laborious and time consuming practice [26].

After the suspension has settled down for a few minutes, it is thoroughly examined using an inverted phase contrast microscope with a minimum of 400-fold magnification. We prefer a microscope equipped with Hoffman contrast modulation because its three-dimensional view is a valuable tool when identifying meiotic cells.

The embryologist should be appropriately trained to identify different stages of meiotic cells. Especially the first meiotic prophase cells are easily identifiable and are usually seen first in individual samples containing very few sperm cells.

Samples containing abundant number of sperm cells can be pooled and divided into small batches for freezing and future use. The samples with low amount of sperm cells should be pooled and frozen separately from the abundant ones. Regardless of the quality and amount of observed sperm cells, the samples should be divided into at least ten straws or ampoules. Freezing can be done according to the sperm freezing protocol most familiar to the clinic, using commercial or home-made freezing media.

On the oocyte retrieval day, a single straw is thawed just before ICSI according to the normal sperm thawing protocol avoiding osmotic shock. Due to the very low number of sperm cells in most of MD-TESE samples, a gradient wash should be avoided, as the few spermatozoa available may be lost. Only a single centrifugation wash (2000–2500 × *g* in conical or round bottom tube) with 3–5 ml of equilibrated cell culture media is performed. After centrifugation, the supernatant is carefully removed, leaving 50–75 µl of media on top of the pellet. Another 50–75 µl of the cell culture media is then added and carefully mixed with the pellet.

Theophylline or pentoxifylline is recommended to mitigate the identification of viable sperm cells for ICSI [27]. The cell suspension is pipetted to form several (5–10) long and narrow droplets on the ICSI dish, without the use of polyvinolpyrrolidone (PVP) solution. A single 10 µl PVP solution droplet is formed to collect the potential sperm cells. The droplets are covered with oil. The suspension droplets are thoroughly searched for viable sperms cells that are collected in the PVP solution droplet to immobilize them to be used in ICSI.

3. Results of MD-TESE

3.1. SRR overall

MD-TESE is proving to be the most effective method of sperm retrieval for men with NOA. The problem with the literature surrounding sperm recovery results in NOA is the lack of uniformity in reporting sperm recovery success [28]. The SRR should only include retrieval of mature spermatozoa viable for ICSI, and collecting round and elongated spermatids should be reported clearly in a separate category.

Another problem with the MD-TESE literature is the lack of patient inclusion criteria in some articles published. The results will be severely distorted with inclusion of men with cryptozoospermia, severe oligozoospermia or medically treated, inadequately followed hypogonadotropic hypogonadism.

Our overall SRR in Turku, Finland is 42% after 180 men operated, the same as after the first 100 cases [26]. We only reported the recovery of mature spermatozoa. The overall figures in the literature show MD-TESE success rate of 40–60% [20], and the large variation maybe due to the reporting issues described.

3.2. Predicting SRR prior to MD-TESE

Serum FSH level is a good predictor of testicular spermatogenetic function, and serves well to distinguish between OA and NOA [29]. In some studies, a higher FSH has been associated with a lower SRR in MD-TESE, but most data suggest that FSH is a poor predictor of MD-TESE success. In a recent meta-analysis, the serum FSH levels in a total of 1261 men with NOA were evaluated. FSH displayed a low predictive value for SRR [30]. In future years, it may be however useful as a part of a multivariable prediction model to more accurately predict SRR prior to MD-TESE [31,32].

Serum testosterone level should be assessed and the testicular production optimized prior to MD-TESE [12]. However, a higher baseline T does not predict a better SRR in MD-TESE [33]. **Serum inhibin B** level may be useful as a part of a predicting model, but as a single variable does not offer any assistance [31].

Testicular volume is in a normal population associated with semen quality [34], and normal testicular volume in azoospermia does imply the possibility of OA [9]. However in men with NOA, testicular size is a poor predictor of SRR, and in our data small testicular volume seemed to be in fact associated with an improved SRR [26]. In a meta-analysis of 1764 cases, no significant threshold for testicular size was found in regard for SRR [30]. Some patient subgroups with excellent SRR have very small testicular volume (e.g. KS), which may explain this finding.

Advanced paternal age has been associated with higher sperm DNA fragmentation, prolonged time to pregnancy, increased miscarriage rate and increased prevalence of certain pathologies of the offspring [35,36]. MD-TESE results however remain good with advancing age [37], but men with KS seem to serve as an exception to this rule [38].

Obesity and elevated BMI of the male partner are associated with

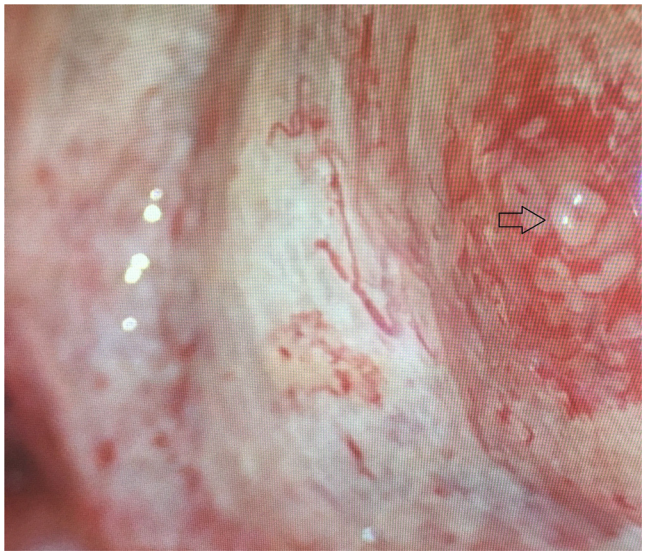

Fig. 2. Microdissection testicular sperm extraction of a man with Klinefelter syndrome shows advanced testicular atrophy with focal remaining tubules (arrow).

higher sperm DNA fragmentation index [39,40], elevated FSH, low T and reduced spontaneous fertility, but obese men seem to have similar SRR in MD-TESE compared to men with normal BMI, in general MD-TESE population as well as in men with KS [40]. There is little data on pregnancy results of MD-TESE-ICSI in obese men, although some reports show worsening of pregnancy outcomes compared to normal weight men [41].

Etiology of azoospermia is an important factor predicting SRR in MD-TESE. Men with **Klinefelter syndrome** (KS) are a subgroup with high chance of sperm recovery in MD-TESE. The very small testicular size and progressive tubular sclerosis leads to low SRR in TESA, but with microscope assisted visualization of the seminiferous tubules, spermatogenesis is easily located (Fig. 2), giving a SRR of 50 to 70% [5,16,42] in MD-TESE. The SRR results may decrease with advancing age [43], but with good results in young adulthood, the current opinion does not support sperm retrieval attempts for teenage boys with KS [44]. Our recommendation would also be to delay surgery until legal adulthood has been reached. **Y chromosome microdeletion** of AZFc region is a diagnosis with good SRR of 60 to 70%, while SRR in Y chromosome deletions in AZFa, AZFb regions or any combination of these will give SRR results dismal enough to call for patient counseling against MD-TESE [45]. **Previous cytotoxic medication or radiation** is generally associated with a good SRR of 50 to 60% [5,46,47], but the conclusive data are missing from subgroups with different cytotoxic agents, amount of radiation and the conditions treated. Sperm cryopreservation remains the most effective method for fertility preservation, but more information is being attained from ongoing research projects surrounding fertility preservation in childhood malignancies [48]. **Cryptorchidism** is associated with reduced fertility and increased risk of testicular malignancy [6,49]. Patients with a previous cryptorchidism form a subgroup with very reassuring MD-TESE results of 64 to 82% [50]. The age at orchidopexy is important for fertility, but the effect on SRR has not been conclusively shown [49,51]. **Idiopathic** NOA is by far the largest subgroup, since no known cause is present in 60 to 70% of NOA. These men have a less favorable prognosis with SRR being 30–40% [26,31,50], but MD-TESE is still more effective than any of other method for surgical sperm recovery[20].

Histopathology is one of the few predictive factors to actually be of assistance in patient counseling prior to MD-TESE [50]. In some cases, a histopathological diagnosis from a previous TESA may be available. Sertoli-cell-only (SCO) is a very common histopathological finding in NOA, and is associated with SRR below average MD-TESE [52]. In our data, the men with previous negative biopsy with SCO had a SRR of 29%, while the men with previous negative biopsy with spermatogenic arrest (maturation arrest, SA) had SRR of 44%. Similar SRR differences are reported in other articles [53–56]. Our histopathological diagnosis does not include classification of early and late maturation arrest, but in a recent article, early maturation arrest was present in twice as many patients undergoing MD-TESE compared with late maturation arrest, with the SRR of 40% and 78%, respectively. SA can also be classified as local or diffuse, with significantly lower SRR in diffuse vs. local SA [57].

3.3. Complications of MD-TESE

Testosterone levels have been shown to decrease after MD-TESE by about 30%, but in 12 to 18 months they recover to baseline in 95% of the patients [58]. MD-TESE is far less traumatic than conventional TESE, and results in fewer infections, hematomas and lower extent of testicular tissue loss [59]. After MD-TESE, testicular ultrasound may show signs of fibrosis and calcification, but these changes are only present in 3–10% of MD-TESE patients at 6 months post operatively [59]. Severe infections are rare, but the use of antibiotic prophylaxis may be useful in preventing them [26]. In our data of 100 men who had MD-TESE performed, we observed two cases of epididymitis and four other infections treated with oral antibiotics, two hematomas that were followed without intervention, and one abscess requiring surgical treatment, giving an overall complication rate of 9% [26]. The use of an antibiotic prophylaxis has however reduced the number of infections in our patients dramatically.

3.4. Pregnancy outcome

Interpreting the data on pregnancy results after MD-TESE is difficult due to the lack of uniform reporting as well as vast differences in TESE-ICSI treatment standards worldwide. Clinical pregnancy rates from ICSI vary between 20 and 50% [60,61]. In our experience, no clear difference is seen in fertilization rates between MD-TESE-ICSI and our general ICSI population [26]. No significant differences are present in pregnancy results in MD-TESE-ICSI of different histopathological patients subgroups [54] (Table 2).

MD-TESE is often combined with synchronized ovarian stimulation of the partner. Some centers have reported that in up to one third of the attempted MD-TESE-ICSI after freezing and thawing, no viable sperm was available for ICSI [62]. There are, in contrast, articles where no such tendency was shown [63]. We have performed all our treatments with frozen-thawed MD-TESE sperm for practical reasons and have not experienced any cases of loss of viable sperm at thawing [26]. We find it therefore difficult to agree with the recommendation to always coordinate an IVF cycle for the female partner. Additional benefits of freezing include easy transport, no need for donor sperm back-up and potential for fertility preservation, as well as minimal need for repeated MD-TESE procedures. This practice has also enabled us to centralize the MD-TESE procedures in Finland, while the couple can still choose to have the ICSI treatment performed at a nearby, easily accessible clinic.

A Belgian study of cumulative live birth rate after sperm recovery by TESE and following ICSI treatments resulted in only 13,5% chance of biological fatherhood for the men with NOA, mainly due to patient drop out [64]. In our ICSI treatment data after the first one hundred MD-TESE operations, only 32 of 42 couples with successful sperm recovery had started the ICSI treatment, and there were live births in 22 families, giving a cumulative live birth rate on 69% for the couples treated with MD-TESE-ICSI. There were two sets of twins. In the group of failed ICSI, four couples had discontinued after only one ICSI cycle and in three couples, the female partner was over 40 years of age. Five young men with KS only had MD-TESE to preserve their fertility, but we did notice a drop out phenomenon also in our data, leading to 22% chance of biological fatherhood for the men operated [26].

Table 2
Sperm recovery rates (SRR) in MD-TESE and cumulative pregnancy rate (cPR) in MD-TESE-ICSI in different testicular histopathological, clinical and genetic diagnoses. MD-TESE = microdissection testicular sperm extraction; ICSI = intracytoplasmic sperm injection.

Author, year	Etiology of non-obstructive azoospermia	SRR in MD-TESE per patient (n)	cPR in MD-TESE-ICSI (n)
Klami, 2018 [26]	Idiopathic, Sertoli cell only	29% (56)	73% (15)
Enatsu, 2016 [56]		19.5% (48)	n/a
Wosnitzer, 2014 [2]		44% (n/a)	46% (n/a)
Kalsi, 2012 [55]		43% (56)	n/a
Klami, 2018 [26]	Idiopathic, spermatogenic arrest	44% (9)	50% (4)
Enatsu, 2016 [56]		27.5%(11)	n/a
Wosnitzer, 2014 [2]		44% (n/a)	29% (n/a)
Kalsi, 2012 [55]		27% (15)	n/a
Klami, 2018 [26]	Klinefelter syndrome	40% (15)	50% (2)
Corona, 2017 [42]		45% (632)	43% (410[a])
Dabaja, 2013 [5]		61%(127)	40% (n/a)
Klami, 2018 [26]	Y chromosome microdeletion AZFc	57% (7)	33% (3)
Wosnitzer, 2014 [2]		72% (n/a)	46% (n/a)
Dabaja, 2013 [5]		67%(152)	46% (n/a)
Klami, 2018 [26]	Chemotherapy or/and radiation	67% (3)	50% (2)
Wosnitzer, 2014 [2]		48% (n/a)	40 (n/a)
Dabaja, 2013 [5]		42%(93)	40% (n/a)
Hsiao, 2011 [47]		37%(73)	48% (27)
Klami, 2018 [26]	Cryptorchidism	90% (10)	86% (7)
Wosnitzer, 2014 [2]		64% (n/a)	50% (n/a)
Dabaja, 2013 [5]		62% (152)	50% (n/a)
Klami, 2018 [26]	Overall	42% (100)	69% (33)
Dabaja, 2013 [5]		52% (1176)	48% (n/a)
Ishikawa, 2012 [24]		51% (851)	n/a

[a] ICSI after conventional TESE included in data.

The initial studies evaluating the health of the children born to men with KS following MD-TESE-ICSI treatment raised concern about the possible increased risk of chromosomal abnormalities in the off spring. However, the more recent studies have proven this concern unsubstantiated and the risk of chromosomal abnormalities not to be elevated [65]. Analysis of the sperm haplotype in men with KS has shown that the sperm contain a normal chromosomal composition [66] (23,X or 23,Y). Men carrying the AZFc microdeletion need to be aware that the Y chromosome with its abnormalities and clinical consequences is directly inherited by all male offspring. It is important to offer all men with a genetic etiology of NOA sufficient genetic counseling prior to MD-TESE [67].

Some uncertainty remains concerning the genetic background of idiopathic NOA. The Y chromosome contains a large proportion of the genes required for normal spermatogenesis. As the Y chromosome is passed on to the male offspring some form of idiopathic NOA may be passed on through MD-TESE-ICSI [68].

4. Discussion

In spite of extensive efforts to predict MD-TESE success, counseling men with NOA prior to MD-TESE remains difficult. Since MD-TESE-ICSI is the most effective option to reach biological fatherhood for the men with NOA, operating these men would be justified even in cases with fairly low SRR. The future studies may succeed in combining several parameters to estimate SRR success for an individual considering MD-TESE. Cost analysis is also needed to help patients and health care providers in making decisions.

The role of medical treatment prior to MD-TESE is not conclusively documented, although there is consensus to aim at optimizing serum T to reach the best MD-TESE results. Furthermore, more data comparing the safety and efficacy of different treatment options is needed in both the general MD-TESE population as well as in different patient subgroups.

Reporting and comparing MD-TESE results is difficult due to some characteristics of the patients operated. Fertility preservation patients form a very unique patient subgroup, which should be excluded from the pregnancy outcome analysis. However, there is a substantial patient drop out also in couples wishing for a child, perhaps due to psychological aspects [69]. This is an issue that should be considered when counseling and treating men with azoospermia. The age of the female partner is another factor affecting the outcome of MD-TESE-ICSI. Couples with a female partner approaching 40 years of age may need to consider opting for donor sperm treatment to achieve the best results.

5. Conclusions

MD-TESE is well documented to be the most effective and safest method to optimize sperm recovery for men with NOA. Since NOA can be diagnosed without testicular biopsy in most cases, MD-TESE should in our opinion be offered as the first line procedure to these men. More data is needed to achieve more accurate prognostic tools to help in preoperative counseling. In experienced hands combined with good quality ICSI, MD-TESE offers some men with NOA a real chance of biological fatherhood.

Conflicts of interest

Rauni Klami: No conflicts of interest.
Harri Mankonen: No conflicts of interest.
Antti Perheentupa: No conflicts of interest.

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