Testicular Sperm Retrieval in Azoospermic Men

Peter Pantke a, Thorsten Diemera, Marcelo Marconia, Martin Bergmannb, Klaus Stegera, Hans-Christian Schuppec, Wolfgang Weidnera,*

a Department of Urology and Pediatric Urology, University of Giessen, Giessen, Germany
b Institute of Veterinary Anatomy, Histology and Embryology, University of Giessen, Giessen, Germany
c Centre for Dermatology and Andrology, University of Giessen, Giessen, Germany

Abstract

Context: Sperm retrieval in combination with IVF/ICSI is the only medical procedure for an azoospermic man to father a child. Different techniques, especially testicular sperm extraction (TESE), have evolved over time and have dramatically improved the outlook for men with testicular azoospermia. However sperm retrieval rates are associated not only with the operation proposed but especially with a distinct pattern of prognostic factors that must be effectively managed for all these infertile patients for their best benefit.

Objectives: To review the etiology, clinical work-up including operative techniques, and prognostic factors for testicular sperm retrieval in azoospermic men to maximin clinical benefit by these procedures.

Evidence Acquisition: Data from basic and clinical studies with a defined, standardized approach pre- and postoperatively were analyzed.

Evidence Synthesis: Different standardized surgical techniques can be offered to extract spermatozoa of azoospermic men from either the epididymis and/or the testis for ICSI. Sperm retrieval offers a treatment for both patients with testicular azoospermia and men with obstructive azoospermia in cases where microsurgical referitilization is not an option or has already failed. Among surgical techniques testicular sperm extraction (TESE) and microsurgical epididymial sperm aspiration (MESA) have become the most popular techniques. However, also percutaneous techniques are employed due their easy feasibility and low costs. By utilizing these techniques together with kryopreservation of extracted spermatozoa a single surgical intervention is able to provide spermatozoa for several ICSI attempts. Extensive surgical interventions in the testis of azoospermic patients have raised concerns about the potential influence on the endocrine compartment of the testis, particularly in patients with small testes and low levels of testosterone.

Conclusions: Testicular sperm retrieval is a feasible and successful procedure. Testicular spermatozoa can be retrieved from the testis in up to 70% of patients, even in cases with testicular azoospermia and severe disorders of spermatogenesis. However, surgical damage of the testis might also compromise the interstitial compartment of the testis with testosterone deficiency as a consequence. Conclusively, endocrine follow-up can be considered mandatory.

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* Corresponding author. Department of Urology and Pediatric Urology, University of Giessen, Rudolf-Buchheim-Str. 7, D-35392 Giessen, Germany. Tel. +49 641 99 44501. Support: Clinical Research Group DFG KFO 18/1 – Male factor infertility due to impaired spermatogenesis – M. Marconi is research fellow of MIDEPLAN, Santiago Chile. E-mail address: Wolfgang.Weidner@chiru.med.uni-giessen.de (W. Weidner).

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1. Introduction

In 1677, van Leeuwenhoek’s medical student Johan Ham made the discovery of “animalcules” in human seminal fluid [1]. For >300 yr, males without spermatozoa in their ejaculate were regarded as infertile. With the introduction of intracytoplasmatic sperm injection (ICSI) in 1992 [2], azoospermic male patients could be offered infertility treatment by surgical sperm retrieval from their reproductive tract. Reproductive technologies were established in numerous laboratories worldwide, and sound pregnancies were reported from ICSI using testicular or epididymal sperm [3–5]. Child birth rates were shown to be similar for sperm that was prepared mechanically or enzymatically or that was cryopreserved [6,7]. Azoospermia defined by repeated evidence of no spermatozoa in semen after centrifugation [8] currently affects 4–10% of male partners in an infertile-couple setting [9].

2. Etiology of azoospermia

For a better pathophysiological understanding of the clinical entity of azoospermia, this condition has been grossly divided into two subgroups: obstructive azoospermia (OA) and nonobstructive azoospermia (NOA). Following this simplified approach, an overview of the underlying etiology can be derived from clinical sperm retrieval reports (Table 1) [5,10]. This paper focuses on testicular NOA.

2.1. Congenital testicular abnormalities

Single-gene or complex genetic disorders affecting testicular function may remain undetected due to insufficient clinical knowledge of their existence and to lack of appropriate detection methods. These causes partially explain the high percentage of idiopathic testicular dysfunction as a major cause in NOA (Table 1). The following genetic disorders are well established.

2.1.1. Cryptorchidism

Correction of cryptorchidism with orchidopexy within the first year of life improves chances for sperm retrieval later in reproductive life [11]. It has been speculated that testicular sperm retrieval rates of 75% in patients with a history of cryptorchidism [11] are due to associated obstructive anomalies of the seminal ducts [12]; however, experimental evidence in the rat suggests that restoration of spermatogenesis after scrotal replacement is attributed to reduced apoptotic germ-cell death [13].

2.1.2. Klinefelter syndrome

The most frequent congenital abnormality with reproductive impairment has been described by Klinefelter [14]. Klinefelter syndrome is diagnosed by chromosome analysis in peripheral blood lymphocytes. Testes are small and firm with an average bitesticular volume <5 ml requiring relatively extensive testicular tissue removal for successful sperm retrieval. Hence, there is an increased risk for postsurgical androgen insufficiency in addition to the endogenous descent of testosterone production over the age of 40 [15]. Because germ cells are lost at puberty with Klinefelter syndrome [16] and probably thereafter, testicular sperm retrieval should be recommended before the critical age of 35 [17]. Recently, high success rates of about 50% from testicular sperm retrieval in Klinefelter patients have been reported [5,18].

2.1.3. Y chromosome microdeletions

Male patients carrying deletions of azoospermia factor (AZF) genes located on the Y chromosome do not show any phenotypic abnormalities other than complete (AZFa, AZFb) or partial (AZFc) disruption of spermatogenesis. Infertile couples may decide for or against screening for a congenital disorder that may be passed on without any other disturbances. If testing is requested, guidelines for a standardized approach should be followed [19]. AZFa and AZFb deletions exclude sperm retrieval [20]. These men are discussed as ideal candidates for spermatogonial stem-cell allotransplantation as foster fathers [21]. Ethical concerns as well as unpredictable risk for infectious or carcinogenic
biological transfer inhibit medical progress in this area.

2.2. Chemical and physical testicular damage

Cytotoxic chemotherapeutic agents primarily affect proliferating type B spermatogonia. After the first course of chemotherapy, type B spermatogonial arrest occurs in most patients 50–60 d later. With additional type A spermatogonial destruction, irreversible azoospermia can ensue [22]. Cyclophosphamide is one of the most aggressive chemotherapeutic agents testis-wise. Cumulative doses of >700 mg/kg result in permanent azoospermia. Lower dose rates may allow for testicular regeneration over a period of ≤4 yr [23].

Other pharmacological agents and industrial toxicants that may reversibly or irreversibly damage testicular stem cells encompass cadmium, carbon disulphide, cyproteronacetate, flutamide, lead, phenytoin, sulfasalazine, valproic acid, and welder vapor [24]. Possible patient exposure and contribution to fertility impairment must be detected through a thorough patient history and a special laboratory investigation.

X-ray radiotherapy resulting in testicular exposure rates of 4 Gy results in testicular azoospermia. Again, recovery of spermatogenesis seems to be possible within approximately 4 yr [24].

2.3. Idiopathic testicular dysfunction

Congenital or acquired damage to the seminiferous tubules follows a common principal pathway of apoptosis [25]. Germ-cell death occurring either spontaneously or due to various aforementioned factors results in similar nonspecific histopathologic patterns [26], described below. Even in severely disturbed spermatogenesis, microscopic foci of mature spermatid formation can be found in the testes [27]. There is currently no valid explanation for the existence of focal areas of intact spermatogenesis in widely dysfunctional seminiferous epithelium. Even in knock-out mice failing to express vital genes for spermatogenesis, it has been shown that spermatid formation is preserved in remote areas despite proven gene silencing [28]. We speculate that some spermatogonial stem cells may harbor alternative pathways of differentiation to compensate for malfunctioning genes. A focal distribution of different histologic patterns within testicular tissue may partly explain high sampling errors. Almost 30% of bitesticular sampling results in discordant histopathologic patterns of both testicles [27].

3. Histopathologic findings in testicular nonobstructive azoospermia

3.1. Hypospermatogenesis

Fig. 1A represents intact tubules. The overall feature of hypospermatogenesis is a reduced number of germ cells, resulting in a decreased number of intact tubules [26]. The degree of hypospermatogenesis can be mild, moderate, or severe.

3.1.1. Maturation arrest

Maturation arrest refers to failure of germ-cell development at any prefinal stage (Fig. 1B). True maturation arrest affects all tubules and typically occurs monomorphically at the spermatocyte stage. Polymorphic maturation arrest affects tubules at different stages of development accompanied by small, intact areas of normal tubular development. Maturational arrest indicates an unfavorable biochemical microenvironment within testicular tissue [29]. Under improved in vitro culture conditions, testicular sperm from patients with premeiotic arrest can proceed to the haploid spermatid stage. Individual cases of successful live birth from ICSI using in vitro developed spermatids have been reported [29].

3.1.2. Sertoli cell-only syndrome

In congenital Sertoli cell-only syndrome (SCO), primordial germ-cell migration into embryonic seminiferous cords is hampered. Solid testicular tissue cords contain orphaned Sertoli cells surrounded by normal intertubular tissue. Congenital SCO can affect the whole testis [30] or can be confined to hypoplastic zones [31]. Sertoli cells remain immature or show abnormal differentiation. Hyaline concretions enveloped by Sertoli cells represent a specific feature of this developmental disorder [31].

In acquired SCO, postnatally damaged testicular tissue shows mature Sertoli cells (Fig. 1C), thickened tubular basal membranes, tubular swelling, shrinkage, and hyalinization [30]. As macrophages immigrate, remnant ghost tubules are demarcated by collagenous fibers and surrounding myofibroblasts [32].

3.1.3. Tubular shadows

Tubules are filled with fibrotic material (Fig. 1D) in association with various degrees of hypospermatogenesis. Tubular shadows are typically found in Klinefelter syndrome, where they may be combined with SCO tubules with or without Leydig cell hyperplasia (Fig. 1E).
3.1.4. Immature testis
Tubules contain immature germ cells and immature Sertoli cells and lack a lumen. This pattern may accompany hypogonadotrophic hypogonadism and, as such, represent a favorable prognosis.

3.1.5. Carcinoma in situ
Preinvasive malignant stem-cell clusters may be seen in tubules with ongoing spermatogenesis (Fig. 1F) or in SCO tubules. Patients with azoospermia display a 2–9% risk for carcinoma in situ (CIS).
With testicular sperm extraction (TESE), collection of biopsy material for exclusion of incidental CIS has been recommended [27].

4. Clinical work-up of azoospermic patients

The clinical setting for OA patients includes normal testicular palpation and ultrasound findings as well as normal serum follicle-stimulating hormone (FSH) and inhibin levels. Further typical features are enlarged and hardened epididymal segments or missing vasa deferentia, such as in congenital bilateral absence of the vas deferens (CBAVD) [9]. Epididymal α-glucosidase may be reduced in seminal plasma [34]. Reconstructive surgery is the primary approach for patients presenting these features [35]. In case of CBAVD and other forms of OA that are not amenable to reconstructive surgery, surgical sperm retrieval, e.g. by epididymal sperm aspiration and consecutive in vitro fertilization–ICSI are indicated.

Diagnostic criteria for NOA may include reduced testicular volume, loss of testicular resilience on palpation, and abnormal ultrasound patterns. Testicular disorders may be combined with phenotypic anomalies as in Klinefelter syndrome [36]. Systemic illness or endocrine disorders [37] adversely affecting testicular function can also be present.

Low levels of gonadotrophins should be detected before carrying out sperm retrieval procedures. In most cases, appropriate endocrine replacement for several months will induce spermatogenesis, allowing for sufficient numbers of sperm to harvest from ejaculation for intrauterine insemination. Prolactin-secreting adenomas require antiprolactinergic therapy [38].

Rarely, endocrine treatment has to be completed by testicular sperm retrieval. If so, sperm retrieval rates of >70% and pregnancy rates of ≤20% can be achieved for male patients who failed to respond to hormonal treatment [39].

FSH levels correlate to the number of SCO tubules [40]. Testicular sperm retrieval rates are poor in male patients with FSH levels >20 IU/l [41]. Similarly, in patients with bitemesticular volume <8 ml, elevated FSH levels >10 IU/l indicate a significantly reduced testicular sperm retrieval yield [42]. According to European Association of Urology (EAU) guidelines, however, high FSH levels alone do not exclude patients from TESE procedures.

In NOA patients, inhibin B levels generally decrease as FSH levels increase. With Sertoli cells being the major source of inhibin B, it seems prudent to use inhibin B plasma levels as prognostic indicators for testicular sperm retrieval. Normal inhibin B levels, however, can be associated with SCO, limiting its diagnostic value for the individual patient [43]. For increasing the predictive probability (P) of sperm retrieval, a formula was calculated from 100 NOA patients that integrates serum inhibin B, FSH, and testosterone (T) levels for increased sensitivity and specificity (P = [1 + exp(5.201 − 0.048 × FSH − 0.449 × T − 0.021 × inhibin B)]−1) [43]. According to the authors, it seemed satisfactory enough for clinical use.

In the future, analysis of metabolomics (e.g., small-molecule metabolites) from tissue samples separated by chromatographic and spectral analysis may help to clearly differentiate OA from NOA or from mixed forms of azoospermia. Using 31P-phosphor-magnetic resonance spectroscopy, significant differences were found in spectra ratios of phosphomonoester to phosphodiesters between healthy and azoospermic men as well as within azoospermic patients [44]. In another study [45] using 1H-magnetic resonance spectroscopy, significant differences in glycerylphosphoryl-ethanol-amine (glycerolphosphoethanolamine) to glycerylphosphorylcholine (glycerolphosphocholine) ratios were found between OA and NOA patients. Metabolomic analysis holds promise for future clinical application.

5. Testicular sperm retrieval techniques

Various techniques for sperm retrieval from the male reproductive tract have been developed (Table 2). In OA, for percutaneous testicular fine needle aspiration (TEFNA), 19-g butterfly needles are placed into the anterior midpole of the testis where

<table>
<thead>
<tr>
<th>Testicular sperm retrieval</th>
<th>PerBiopsy</th>
<th>Percutaneous testicular gun biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEFNA</td>
<td></td>
<td>Testicular fine needle aspiration</td>
</tr>
<tr>
<td>TESE (unifocal, multifocal)</td>
<td></td>
<td>Testicular sperm extraction</td>
</tr>
<tr>
<td>Loup-TESE</td>
<td></td>
<td>Loup-assisted TESE</td>
</tr>
<tr>
<td>M-TESE</td>
<td></td>
<td>Microscopic TESE</td>
</tr>
<tr>
<td>Cryo-TESE</td>
<td></td>
<td>TESE for cryopreservation</td>
</tr>
<tr>
<td>Onco-TESE</td>
<td></td>
<td>TESE from testicular tumor patients</td>
</tr>
<tr>
<td>Re-TESE</td>
<td></td>
<td>Repetitive TESE</td>
</tr>
<tr>
<td>Posttesticular sperm retrieval</td>
<td>PESA</td>
<td>Percutaneous epididymal sperm aspiration</td>
</tr>
<tr>
<td></td>
<td>MESA</td>
<td>Microscopic epididymal sperm aspiration</td>
</tr>
<tr>
<td></td>
<td>VASA</td>
<td>Vas sperm aspiration</td>
</tr>
</tbody>
</table>
suction can be applied by pulling back on the plunger of a 30-cm³ syringe. While redirecting the tip of the needle within testicular tissue, return of opaque material in the butterfly tubing can be observed. The procedure can safely be performed under local anesthesia, causing less damage to subtunical blood vessels than unilocular or multilocular open procedures [46]. The use of ultrasound-guided testicular sperm aspiration for visualization of major vessels to largely avoid postaspiration subtunical testicular bleeding [47] has not gained widespread acceptance. TEFNA is successful in OA [48,49]; therefore, most laboratories use this technique in OA patients. Other groups rely on automatic biopsy guns, called PercBiopsy, by firing biopsy needles into the testis.

In NOA, TESE in a trifocal manner is routine in our group in Giessen, Germany, whereby both testicles are delivered from the vaginal tunica and avascular regions of the upper, middle, and lower anterior surface of the albuginea tunica are incised over 0.5–1 cm (Fig. 2). Under gentle testicular pressure, small protruding pieces (50–750 mg [55,56]) of testicular tissue can be harvested using fine surgical scissors [50].

Alternatively, an equatorial scrototomy with multiple biopsies collected in an equatorial manner around the testis has been described [42]. With respect to the vascular architecture of the testis, this transverse approach is preferred to a longitudinal incision of the tunica albuginea for avoiding subtunical blood vessel damage [51]. Biopsy material can be cryopreserved for later use (cryo-TESE).

Perioperatively wet preparations can be transferred to the in vitro fertilization (IVF) lab for immediate use or can serve as indicators of successful sperm retrieval to limit the extent of testicular surgical manipulation. For wet preparations, testicular tissue is harvested in a temperature-adopted culture medium and shredded with glass slides and fine forceps for separation of individual tubules under stereomicroscope at ×40 magnification. Further mincing under phase contrast microscopy at ×200–400 magnification allows for the detection of elongated spermatids [10]. As soon as spermatooza are identified, no further testicular incisions are made.

With increased numbers of incisions, chances increase for retrieving sperm [52]. In OA, testicular tissue is successfully extracted on an unifocal basis, whereas in NOA, between 3 and 10 incisions have been recommended [5]. With more incisions, more tissue is removed. It is still under debate whether successful retrieval correlates to the number of incisions or simply to the total amount of tissue harvested.

The presence of blood vessels in peripheral testicular regions may indicate residual spermatogenic areas in NOA [53]. One case report demonstrated the association between intraoperative laser Doppler scanning for the detection of testicular blood flow and sperm retrieval [54]. The application of ultrasound has not become a universal standard. Recently, the concept of microscopic sperm extraction has gained wide acceptance. In microscopic TESE (M-TESE) using optical ×20–25 magnification, individual seminiferous tubules can be identified. Because many features of testicular dysfunction are accompanied by heterogeneous sizing of tubules, tissue sampling can be restricted to the largest tubules that most likely contain the full range of spermatogenic cells. It has been claimed from the original report on M-TESE that up to 70-fold of smaller volumes of testicular specimens that are microdissected can yield better results than conventional biopsies [55]. Table 3 highlights comparative reports on sperm retrieval using M-TESE as compared with conventional testicular sampling methods. M-TESE can be expected to yield significantly higher sperm retrieval rates in patients with hypospermatogenesis and other forms of mixed pathology with concomitant heterogeneous tubular sizing [56,57] as compared to conventional TESE.
This working hypothesis, however, awaits final proof.

M-TESE allows for microbipolar coagulation as well as for less traumatic microsurgical suturing of the tunica albuginea. Postoperative intratesticular pressure is more likely to remain at a physiological level [62]. Respecting the vascular anatomy, limited hematoma formation quickly resolves with time [63]; however, if previous TESE procedures failed to harvest sperm, reinterventions should be microscopically assisted [61].

Poor sperm retrieval rates can generally be improved by repetitive TESE (re-TESE) [10]. With repetitive or multilocular sperm extractions, testosterone blood levels transiently decline within 6 mo in 40% of all patients [64]. There is currently no information as to what the endocrine capacity for tissue removal would be. On average, follow-up periods of 2 yr are recommended for detection of any permanent hypogonadic state [64]. In Klinefelter patients and after extensive re-TESE, life-long follow-up is recommended.

### Table 3 – Sperm retrieval rate (SRR) in patients with nonobstructive azoospermia after testicular sperm extraction (TESE) compared to microscopic TESE (M-TESE)

<table>
<thead>
<tr>
<th>n TESE/M-TESE</th>
<th>SRR TESE (amount of tissue removed)</th>
<th>SRR M-TESE (amount of tissue removed)</th>
<th>Advantage M-TESE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>37/56</td>
<td>35% (−3 × 50 mg)</td>
<td>43% (≥3 × 10−15 mg)</td>
<td>+8%</td>
<td>[58]</td>
</tr>
<tr>
<td>100/100</td>
<td>30% (Unifocal 54 ± 27 mg)</td>
<td>47% (5 ± 3 mg)</td>
<td>+17%</td>
<td>[56]</td>
</tr>
<tr>
<td>22/27</td>
<td>45% (250−750 mg)</td>
<td>63% (−2−10 mg)</td>
<td>+18%</td>
<td>[55]</td>
</tr>
<tr>
<td>83/460</td>
<td>32% (−500 mg)</td>
<td>57% (−2−10 mg)</td>
<td>+25%</td>
<td>[57]</td>
</tr>
<tr>
<td>24/74</td>
<td>17% (−150 mg)</td>
<td>45% (20−100 mg)</td>
<td>+28%</td>
<td>[59]</td>
</tr>
<tr>
<td>176/176</td>
<td>17% (Variable 1–4 biopsies)</td>
<td>50% (−2−10 mg)</td>
<td>+33% a</td>
<td>[60]</td>
</tr>
<tr>
<td>46/46</td>
<td>0% (Failed TESE elsewhere)</td>
<td>46% (−10−15 mg)</td>
<td>+46% a</td>
<td>[61]</td>
</tr>
</tbody>
</table>

* Repeated sperm retrieval procedure: Advantage of M-TESE has to be corrected by SSR that would have been achieved with repetitive TESE.

### Table 4a – Probability of sperm retrieval from testicular sperm extraction in azoospermic males

<table>
<thead>
<tr>
<th>Preoperative prognostic factor</th>
<th>Probability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical obstructive azoospermia</td>
<td>100%</td>
<td>[10]</td>
</tr>
<tr>
<td>Partial disruption of spermatogenesis (AZFc deletion)</td>
<td>75%</td>
<td>[20]</td>
</tr>
<tr>
<td>History of cryptorchidism</td>
<td>74%</td>
<td>[11]</td>
</tr>
<tr>
<td>History of hypogonadotrophic hypogonadism</td>
<td>73%</td>
<td>[39]</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>57%</td>
<td>[5]</td>
</tr>
<tr>
<td>Testicular tumor</td>
<td>45%</td>
<td>[65]</td>
</tr>
<tr>
<td>Postgonadotoxic therapy</td>
<td>45%</td>
<td>[22]</td>
</tr>
<tr>
<td>Small testicles, high follicle-stimulating hormone values</td>
<td>29%</td>
<td>[42]</td>
</tr>
<tr>
<td>Complete disruption of spermatogenesis (AZFa, AZFb deletions)</td>
<td>0%</td>
<td>[20]</td>
</tr>
</tbody>
</table>

AZF = azoospermia factor.

### 6. Prognostic factors for testicular sperm retrieval

#### 6.1. Preoperative factors

Chances for sperm retrieval from TESE in relation to various clinical and endocrine parameters are summarized in Table 4a. Higher fertility rates can be expected in OA patients than in NOA patients, with birth rates of approximately 47% and 21%, respectively [42].

#### 6.2. Postoperative factors

With severe testicular dysfunction indicated by low numbers of tubules with elongated spermatids, chances for pregnancy become very low (Fig. 3; Table 4b); therefore, a classification system based on the number of intact tubules per total number of tubules counted is suggested for grading TESE samples [26]. Since the traditional Johnsen scoring system [67] for classification of testicular biopsies is based on a mean score for tubular development, it has turned out to be a poor prognostic factor for sperm retrieval procedures [27].
In applying reverse transcription–polymerase chain reaction (RT-PCR) on testicular biopsies, few numbers of intact tubules are sufficient for amplification and detection of several postmeiotic gene transcripts that indicate the presence of elongated spermatids. RT-PCR allows for screening of 1–2 ml of testicular tissue samples because it is much more sensitive than histopathologic evaluation based on sample size in the range of 1–2 μl. Molecular markers such as DAZ (deleted in azoospermia) [68,69], RNA-binding motif (RBM) [68,69], transition protein-1 (TP-1) [70], and protamines [66,68–72] are currently under investigation for indicating testicular dysfunction.

Protamines play a key role for correct spermatid differentiation by ensuising chromatin condensation in elongated spermatids. Lack of protamine gene expression results in infertility [66]. Additionally, testicular dysfunction based on abnormal protamine expression resulting in aberrant chromatin condensation may not necessarily be accompanied by abnormal sperm morphology and, as such, may not be recognized with conventional histologic evaluation [71].

7. Conclusions

A current approach to azoospermia is summarized in Fig. 4. For presumed OA, percutaneous testicular sperm retrieval is highly successful. In case OA cannot be confirmed on testicular histology, proceed to TESE or M-TESE [42], as is the primary approach for presumed NOA. TESE can be started on one testicle on a unifocal basis. Intraoperative wet preparations [10] are helpful in deciding whether to extend the number of tunical incisions and for proceeding to the second testicle. CIS should always be ruled out for both sides [27]. TESE can be repeated many times; however, endocrine follow-up is necessary for detection of testicular hypogonadism.

The most advanced, developed region of the testis is a valuable predictor of successful sperm retrieval. As soon as intact tubules are found next to abnormal ones, the actual testicular pattern should be classified as hypospermatogenic, even when the predominant tubular feature may be SCO or maturation arrest [27]. A classification system based on the number of intact tubules with elongated spermatids is suggested for grading TESE samples [41].

Comprehensive genetic counseling is mandatory for infertile couples deciding for assisted reproduction, since genetic disorders, as yet undetected, may be passed on to the following generation with multiplying variety.
Conflicts of interest
The authors have nothing to disclose.

References


CME questions

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1. Which statement is false about the single most effective treatment indication for TESE in non-obstructive azoospermia ?
   A. Low testicular volume and high FSH levels
   B. AZF c deletion
   C. Hypogonadotrophic hypogonadism
   D. History of unsuccessful TESE sampling

2. What kind of testicular histopathology may accompany a favourable prognosis for treatment of infertility ?
   A. Immature testis
   B. Monomorphic maturation arrest
   C. Congenital Sertoli cell only syndrome
   D. All

3. Which statement is false about TESE techniques ?
   A. Longitudinal tunical incisions are preferred over transverse incisions.
   B. Multifocal tunical incisions always yield higher sperm retrieval rates than unifocal tunical incisions.
   C. M-TESE always yields higher sperm retrieval rates as compared to conventional TESE.
   D. All

4. Concerning prognosis for TESE: which factor is most favourable ?
   A. AZF c deletions
   B. Lack of protamine gene expression
   C. Klinefelter syndrome
   D. History of chemotherapy
5. Concerning hypogonadism after TESE: which is the highest risk factor?
   A. Carcinoma in situ
   B. Klinefelter syndrome
   C. History of cryptorchidism
   D. Congenital bilateral absence of the vas – failed reconstruction

6. Which overall percentage of birth rates after TESE/ICSI can be expected from azoospermic patients (non-obstructive/obstructive)?
   A. 40%/25%
   B. 25%/40%
   C. 10%/40%
   D. 40%/40%