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EAU Guidelines

European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2025 Update on Male Infertility

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Abstract

Background and objective: To present a summary of the updated 2025 European Association of Urology (EAU) Guidelines on Sexual and Reproductive Health (SRH) on male infertility, providing practical recommendations on the clinical work-up with a focus on diagnosis, treatment and follow-up. Methods: For the 2025 SRH guidelines, new and relevant evidence was identified, col- lated, and appraised via a structured assessment of the literature. Databases searched included Medline, EMBASE, and the Cochrane Libraries. Recommendations within the guidelines were developed by the panel to prioritise clinically important care decisions. The strength of each recommendation was determined according to a balance between desirable and undesirable consequences of alternative management strategies, the qual- ity of the evidence (including the certainty of estimates), and the nature and variability of patient values and preferences. Key findings and limitations: Key recommendations emphasise the importance of a thor- ough urological assessment of all men seeking medical help for fertility problems to ensure appropriate treatment. The guidelines also stress the clinical relevance of a

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parallel investigation of the female partner during the diagnostic and management work-up of the infertile couple, to promote shared-decision making in terms of timing and therapeutic strategies. Furthermore, the guidelines recommend to counsel all infer- tile men and men with abnormal semen parameters on the associated health risks. Key changes in the male infertility guidelines for 2025 include: the addition of two new sections addressing exome sequencing and probiotic treatment; and significant update of the evidence base and recommendations for the diagnostic work-up of male infertility. Conclusions and clinical implications: This overview of the 2025 SHR guidelines offers valuable insights into the diagnosis, classification, treatment and follow-up of male fac- tor infertility and are designed for effective integration into clinical practice.

1. Introduction

We present a summary of the updated European Association of Urology (EAU) guidelines on sexual and reproductive health (SRH) in relation to male infertility. The aim is to provide practical recommendations for clinical management of male infertility in a multidisciplinary team, with a focus on diagnosis, treatment and follow-up.

It must be emphasised that clinical guidelines present the best evidence available to experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather facilitate decisions that also take into account the personal values and individual circumstances of each patient. Guidelines are not mandates and do not purport to be a legal standard of care.

2. Methods

For the 2025 SRH guidelines, new and relevant evidence was identified, collated, and appraised via a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the SRH guidelines was performed. The detailed search strategy is available online (https://uroweb.org/guidelines/sexual-and-reproductive-health/publications-appendices).

Recommendations in the guidelines were developed by the panel to prioritise clinically important shared care deci- sions. The strength of each recommendation is determined by the balance between desirable and undesirable conse- quences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nat- ure and variability of patient values and preferences. Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate that only lower-quality evidence was available, and/or an equivocal balance between benefit and harm, and uncertainty or variability for patient preferences [1].

3. Guidelines

3.1. Epidemiology and aetiology

Infertility is defined as the inability of a sexually active couple not using contraception to achieve spontaneous pregnancy within 12 mo [2]. Approximately 15% of couples do not achieve pregnancy within 12 consecutive months and seek medical treatment for infertility [3]. One in eight cou- ples encounter problems when attempting to conceive a first child (primary infertility), and one in six when attempting to conceive a subsequent child (secondary infer- tility) [4]. In 50% of involuntarily childless couples, a male- associated factor is found, usually together with abnormal semen parameters [2]. Table 1 summarises the main male infertility causes and associated factors [5]. However, in 30–40% of cases, no male-associated factor is found that could explain the underlying impairment of sperm parame- ters, which was historically referred to as idiopathic male infertility.

Table 2 lists the guideline recommendations in relation to the epidemiology and aetiology of male infertility.

3.2. Diagnostic workup

A focused evaluation of male patients should include: a medical and reproductive history; physical examination; semen analysis—with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [6,7]—and hormonal evaluation [8]. Other investigations (eg, genetic analysis and imaging) may be required, depending on the clinical findings and semen parameters.

Semen analysis plays a central role in the diagnostic assessment of male infertility and provides important information regarding sperm quality; however, clinicians should counsel infertility patients that semen analysis alone cannot be used to distinguish fertile from infertile men (Table 3) [9]. If semen analysis is normal according to WHO criteria, a single test is sufficient. If the results are abnormal on at least two tests, further andrological investigation is indicated.

3.2.1. Measurement of oxidative stress

Oxidative stress is an important factor in male infertility as it affects sperm quality and function, as well as the integrity of sperm [10]. Oxidative stress may lead to sperm DNA damage and reduced DNA integrity, which are associated with lack of fertilisation, poor embryo development, mis- carriage, and implantation failure [11,12]. Oxidative stress is generally associated with poor lifestyle (eg, smoking) and environmental exposure; therefore, antioxidant regi- mens and lifestyle interventions may mitigate the risk of

Table 1 – Male infertility causes, associated factors, and percentage distribution in 10 469 patients [5]

Diagno sis	Unselec ted patient s (n = 12 945)	Azoos permic patients (n = 1446)
Cohort (%)	100 42.6 8.4	
Infertility of known (possible) cause (%)	14.8 3.9 1.2	11.2
Maldescended testes	5.0 30.0 10.1	42.6
Varicocele	2.6 0.1 2.3 1.6	17.2
Sperm autoantibodies	0.3 0.4 <0.1	10.9
Testicular tumour	2.2 1.4 0.8 2.2	–
Other	7.8 5.0 1.5 0.7	2.8
Idiopathic infertility	0.6 2.4 2.2 0.9	1.2
Hypogonadism	0.5 0.8	13.3
Klinefelter syndrome (47, XXY)		16.4
XX male		13.7
Primary hypogonadism of unknown cause		0.6
Secondary (hypogonadotropic) hypogonadism		0.8
Kallmann syndrome		1.9
Idiopathic hypogonadotropic hypogonadism		0.5
Residual after pituitary surgery		0.4
Late-onset hypogonadism		0.3
Constitutional delay of puberty		– –
Other		0.8
General/systemic disease		0.5
Cryopreservation because of malignant disease		12.5
Testicular tumour		4.3
Lymphoma		4.6
Leukaemia		2.2
Sarcoma		0.9
Disturbance of erection/ejaculation		–
Obstruction		10.3
Vasectomy		5.3
Cystic fibrosis (congenital bilateral absence of vas deferens)		3.0
Others		1.9

Table 2 – Recommendations for epidemiology and aetiology of male infertility

Rec ommendat ion	Strength rating
Perform infertility evaluation in couples who have not conceived after 12 consecutive months of regular, unprotected intercourse.	Strong
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Investigate all men belonging to couples seeking medical help for fertility problems.	Strong

DNA fragmentation and improve sperm quality [13], but high-quality evidence from randomised controlled trials (RCTs) is lacking. Although reactive oxygen species (ROS) can be measured via various assays (eg, chemilumines- cence), no standardised testing methods are available and routine measurement of ROS requires validation in well- designed RCTs [14]. The current EAU guidelines do not rec- ommend routine testing of ROS.

3.2.2. Measurement of the sperm DNA fragmentation index

No studies have unequivocally and directly tested the impact of sperm DNA fragmentation (SDF) on the clinical management of infertile couples. However, SDF is more common in infertile men and has been identified as a major contributor to male infertility that negatively affects natural pregnancy rates [15] and is associated with poorer outcomes following assisted-reproductive technology (ART) [16,17], including impaired embryo development [16], miscarriage, recurrent pregnancy loss [18–20], and birth defects [16].

Several assays for SDF measurement have been described. It has been suggested that current methods for assessing sperm DNA integrity still do not reliably predict ART outcomes and there is controversy over whether to recommend these assay for routine clinical use [17,21,22]. However, there is evidence in support of SDF measurement for couples with recurrent pregnancy loss after natural conception and failure of ART and for men with unexplained infertility [17,19].

Testicular sperm has lower SDF levels than ejaculated sperm [23] and the use of testicular sperm for intracytoplas- mic sperm injection (ICSI) has been associated with poten- tially better outcomes in comparison to ejaculated sperm for men with high SDF [23,24]. A meta-analysis suggested that testicular sperm extraction (TESE) for ICSI may improve ART outcomes, but there was significant heterogeneity for the data and the authors suggest that RCTs are needed to validate the use of TESE in men with elevated SDF [25].

Clinicians may offer the use of testicular sperm for ART to fully informed patients with high SDF on a case-by-case basis once they are aware of the low level of evidence for this approach and after a full discussion that includes reproductive specialists. Furthermore, testicular sperm should only be used in this setting once the common risk factors for elevated SDF have been excluded and other treatments to reduce SDF have failed.

Table 3 – Lower reference limits (5th centile and corresponding 95% CI) for semen characteristics

Parame ter	2021 Lower reference limit (95% CI) [a]
Semenvolume(ml)	1.4(1.3–1.5)
Totalspermnumber(106/ejaculate)	39(35–40)
Spermconcentration(106/ml)	16(15–18)
Totalmotility(PR+NP,%)	42(40–43)
Progressivemotility(PR,%)	30(29–31)
Vitality(livespermatozoa,%)	54(50–56)
Spermmorphology(normalforms,%)	4(3.9–4.0)
Other consensus threshold values	
pH	>7.2
Peroxidase-positiveleukocytes(106/ml)	<1.0
Tests for antibodies on spermatozoa	
MARtest(motilespermatozoawithboundparticles,%)	Noevidence-basedreferencevalues;eachlaboratoryshoulddefineits normal reference ranges by testing a sufficiently large number of normal fertile men.
Immunobeadtest(motilespermatozoawithboundbeads,%)	Noevidence-basedreferencelimits.
Accessory gland function	
Seminalzinc(lmol/ejaculate)	≥2.4
Seminalfructose(lmol/ejaculate)	≥13
Seminalneutrala-glucosidase(mU/ejaculate)	≥20

CI = confidence interval; MAR = mixed antiglobulin reaction; NP = nonprogressive; PR = progressive (a + b motility).
[a] Distribution of data from the population is presented with one-sided intervals (extremes for the reference population data). The lower 5th percentile represents the level under which only results for 5% of the men in the reference population were found.

3.2.3. Hormonal determinations

Male infertility is frequently linked to hypogonadism, and biochemical screening is recommended as part of the diagnostic evaluation because of long-term implications for cardiometabolic health, including metabolic syndrome and higher cardiovascular risk [26]. Therefore, measurement of serum total testosterone, follicle-stimulating hormone (FSH), and luteinising hormone (LH) is the basic hormonal workup for infertile man (Table 4). In general, FSH levels are negatively correlated with the number of spermatogo- nia [27]. However, for azoospermic patients undergoing TESE, FSH levels do not accurately predict the presence of spermatogenesis, as men with maturation arrest on histology can have normal FSH and testicular volume [28,29]. In addition, growing evidence suggests that lower preopera- tive serum anti-Müllerian hormone (AMH) levels are associ- ated with a higher likelihood of positive sperm retrieval (SR) outcomes in men undergoing microdissection TESE (mTESE) [30,31].

3.2.4. Genetic testing

Genetic testing is of critical importance in the management and counselling of infertile males. The frequency of genetic anomalies appears to be related to the degree of spermatogenic dysfunction, and it has been demonstrated that nonobstructive azoospermia (NOA) is associated with the highest prevalence of chromosomal abnormalities [32,33].

Karyotype abnormalities are the most prevalent genetic factors contributing to male infertility [34]. These abnormalities often involve chromosomal numerical anomalies, such as Klinefelter syndrome, which is characterised by the presence of additional X chromosomes. Klinefelter syndrome has a variable clinical presentation [35]. Similarly, the presence of germ cells or spermatogenesis is highly variable among men with Klinefelter syndrome, but it has been demonstrated that TESE can retrieve sperm in 20–50% of cases [35,36]. Structural anomalies (deletions, duplications, inversions of a region of an autosomal or sex chromosome) such as a Robertsonian translocation may also result in impaired or absent spermatogenesis. In comparison to the general population, the incidence of mainly autosomal structural abnormalities is tenfold higher for patients with a sperm count <5 million/ml (4%) [32,33]. Men with NOA are at highest risk, especially for sex chro- mosomal anomalies [37,38]. For this reason, the guidelines advocate karyotype testing for patients with azoospermia and those with a sperm concentration of <5 million/ml.

Microdeletions of the Y chromosome, termed AZFa, AZFb, and AZFc deletions, are the second most common genetic cause of male infertility. AZFc deletions are most common (65–70%), followed by Y-chromosome deletions of the AZFb, AZFb + AZFc, or AZFa + AZFb + AZFc regions (25–30%). AZFa region deletions are rare (5%) [39]. Complete deletion of the AZFa region is associated with Sertoli cell–only syndrome (SCOS), while complete deletion of the AZFb region is asso- ciated with spermatogenic arrest. Complete deletions of the AZFa and AZFb regions predict poor prognosis for surgical SR, and therefore TESE should not be attempted in these patients [40]. By contrast, deletions of the AZFc region are associated with variable clinical presentation that can include oligospermia or azoospermia, and sperm can be successfully retrieved via TESE in 53–75% of these men [41]. As Y-chromosome microdeletions are absent in men with normal sperm parameters and are rare in men with a sperm concentration >5 million/ml, the guidelines recom- mend microdeletion testing in infertile men with a sperm concentration of <5 million/ml, but consider it mandatory for those with azoospermia or a sperm concentration <1 million/ml.

Cystic fibrosis is the most common autosomal recessive disorder in the Caucasian population [42]. Approximately 2000 CFTR mutations have been identified, and any CFTR alteration may lead to congenital bilateral absence of the vas deferens (CBAVD), which has been detected in approxi-

Table 4 – Recommendations for diagnostic workup of male infertility

Recommendation	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of an infertile male, since this might determine decision-making in terms of timing and therapeutic strategies (eg, ART vs surgical intervention).	Strong
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters.	Strong
Take a complete medical reproductive and family history, assess lifestyle and behaviour risk factors, and conduct a physical examination and semen analysis.	Strong
Counsel infertile men and men with abnormal semen parameters on the associated health risks.	Weak
Assess testicular volume using a Prader orchidometer or viatesticular US.	Weak
Perform semen analyses according to the latest edition of the WHO manual for the examination and processing of human semen.	Strong
Perform at least two consecutive semen analyses if the baseline analysis is abnormal.	Strong
Do not routinely use measurement of reactive oxygen species in the diagnosis and management of the male partner of an infertile couple.	Weak
Perform SDF testing in the assessment of couples with recurrent pregnancy loss from natural conception and failure of ART and for men with unexplained infertility.	Strong
Consider the use of testicular sperm for ICSI in patients with high SDF in ejaculated sperm as an experimental option.	Weak
Perform a hormonal evaluation including at least serum total testosterone and follicle-stimulating hormone/luteinising hormone in all cases of oligozoospermia and azoospermia.	Strong
Offer standard karyotype analysis and genetic counselling to all men with azoospermia or oligozoospermia (spermatozoa <5 million/ml) for diagnostic purposes.	Strong
Provide long-term endocrine follow-up and appropriate medical treatment to men with Klinefelter syndrome.	Strong
Perform Y-chromosome microdeletion testing in men with sperm concentrations of ≤1 million sperm/ml. Consider this testing in men with sperm concentrations of <5 million sperm/ml.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with ICSI that microdeletions will be passed on to sons.	Strong
Do not perform testicular sperm extraction in patients with complete deletions that include the AZFa and AZFb regions.	Strong
Test men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal anomalies) and their partners for CFTR gene mutations.	Strong
Provide genetic counselling for all couples with a genetic abnormality found on clinical or genetic investigation and for patients who carry a (potential) inheritable disease.	Strong
Perform scrotal US in men with infertility, as they have a higher risk of testis cancer.	Weak
Discuss invasive diagnostic modalities (eg, US-guided testicular biopsy with frozen section vs radical orchidectomy vs surveillance) in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present, in a multidisciplinary team setting.	Weak
Perform transrectal US if a partial or complete distal obstruction is suspected.	Strong

ART = assisted reproductive technology; ICSI = intracytoplasmic sperm injection; SDF = sperm DNA fragmentation; US = ultrasound; WHO = World Health Organization.

mately 1% of infertile men and in up to 6% of men with obstructive azoospermia (OA) [43]. All men with azoospermia should be carefully examined to exclude CBAVD, particularly those semen volume <1.0 ml and acidic pH <7.0 [44–46]. According to the guidelines, men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), along with their partner, should undergo testing for CFTR mutations.

The diagnostic yield of whole-exome sequencing in males with NOA is rapidly increasing and is revealing monogenic causes of male-factor infertility, genetic variants that may impact the function of genes with potential involvement in male factor infertility, and candidate genes [47,48]. Different case-control series of exome sequencing in men with motility and morphology disorders have iden- tified significant genetic variants that could be incorporated into panels for ciliopathy/sperm flagellum phenotypes or specific sperm morphology traits, highlighting the impor- tance of genotyping in the diagnosis of severe male factor infertility conditions [49,50]. The findings suggest that the introduction of exome sequencing in idiopathic infertility and NOA will improve diagnosis and possible management of patients, although the clinical application of these tests is not clear.

3.2.5. Imaging in infertile men

In clinical practice, estimation of testicular volume using a Prader orchidometer is a good surrogate for volume measured via ultrasound (US), and is easier to perform and cost effective [5]. Nevertheless, scrotal US has a relevant role for the following:

- Testicular volume assessment in selected cases, such as large hydrocele, inguinal testis, epididymal enlargement/fibrosis, thickened scrotal skin, and small testis, in which the epididymis is large in comparison to the total testicular volume [51,52].
- Assessment of testicular anatomy and structure in terms of US patterns for detection of signs of testicular dysgenesis often related to impaired spermatogenesis (eg, non-homogeneous testicular architecture and microcalcifications).
- Detection of testicular tumours, for which infertile males are at higher risk
- Finding indirect signs of obstruction such as dilatation of the rete testis, an enlarged epididymis with cystic lesions, or an absent vas deferens [52].

Men with infertility have a higher risk of testicular cancer in comparison to fertile men (pooled odds ratio [OR] 1.91, 95% confidence interval [CI] 1.52–2.42) [53]. Moreover, oligozoospermic men had a higher risk of cancer in comparison to fertile control subjects (hazard ratio 11.9) [54] and the prevalence of testicular cancer was approximately 18-fold higher for men with testicular microcalcification (TM) [55]. There is currently no clear evidence regarding the cost/benefit ratio for routine use of US screening for infertile men, and this imaging may result in over-

diagnosis of incidental testicular masses, of which a significant proportion will be indeterminate and require further surveillance or intervention.

There are no definitive US size criteria to distinguish between benign and malignant testicular lesions, but data suggested that a lesion size of < 5 mm is more likely to be benign [56]. On scrotal US for postpubertal men, the odds of malignancy were significantly lower for heterogeneous versus homogeneous masses, hyperechogenic versus hypoechogenic masses, normal versus elevated enhancement, and peripheral versus central vascularity [56]. Small hypoechoic/hyperechoic areas may be diagnosed as intratesticular cysts, focal Leydig-cell hyperplasia, fibrosis, or focal testicular inhomogeneity after previous pathological conditions. Hence, these findings require careful periodic US assessment and follow-up, especially in patients with additional risk factors for malignancy (infertility, bilateral TM, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of/contralateral tumour) [52]. Although histological diagnosis remains the clinical standard in differentiating benign from malignant lesions, the majority of testicular lesions identified incidentally during workup for infertility will be benign, and thus testicular biopsy may be considered as overinvestigation [57]. Therefore, a multidisciplinary team approach should be adopted, with consideration of risk stratification for malignancy, including interval growth of the lesion and US prognostic features (eg, size >5 mm, echogenicity, and vascularity of the lesion).

Varicoceles are commonly detected during a physical examination; however, colour Doppler US can confirm the diagnosis and provide additional metrics, such as the presence of venous reflux and venous diameter. This helps in differentiating radiologically significant varicoceles, which are characterised by a venous diameter >3 mm in both the upright position and during the Valsalva manoeuvre, as well as a venous reflux duration exceeding 2 s [58]. Likewise, scrotal US is used to assess for the presence or absence of the vas deferens and seminal vesicles, and any epididymal abnormalities [59,60]. In addition, transrectal US may be useful in identifying ejaculatory duct cysts, obstructions, dilatation, and atrophy or hypoplasia of the seminal vesicles in men with azoospermia [52,61].

3.3. Special conditions and relevant clinical entities

3.3.1. Cryptorchidism

Cryptorchidism affects approximately 1% of all infants [62]. It has been postulated that cryptorchidism may be a part of testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy, including exposure to endocrine-disrupting chemicals. Besides cryptorchidism, TDS includes hypospadias, lower fertility, higher risk of malignancy, and dysfunction of Leydig/Sertoli cells [63]. The degeneration of germ cells in maldescended testes is apparent even after the first year of life and varies according to the position of the testes [64]. During the sec- ond year of life, the number of germ cells further declines. Therefore, treatment between the age of 6 mo and 18 mo is recommended to conserve spermatogonial stem cells, safeguard future spermatogenesis and hormone production, and reduce the risk of tumours [65]. Surgical treatment is the most effective approach. Meta-analyses on the use of medical treatment with gonadotropin-releasing hormone (GnRH) and human chorionic gonadotropin (hCG) have demonstrated poor success rates [66,67].

In men with a unilateral undescended testis, the contralateral normal descended testis may also have structural abnormalities, including smaller volume, softer consistency, and lower results for markers of future fertility potential (spermatogonia/tubule ratio and dark spermatogonia) [68,69]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

Paternity rates among men with a history of unilateral cryptorchidism are nearly equivalent to those for men without cryptorchidism. However, those with a history of bilateral cryptorchidism have a paternity rate of 35–53%, and these individuals should be counselled accordingly [70]. In addition, men with cryptorchidism may be at higher risk of hypogonadism [71] and testicular cancer, and should be encouraged to perform regular self-examinations [72]. The risk of a germ cell tumour is 3.6–7.4 times higher for men with cryptorchidism than in the general population, and 2–6% of men with a history of cryptorchidism will develop a testicular tumour [62]. Orchidopexy performed before the onset of puberty can reduce the risk of testicular cancer [73]. However, there is evidence to suggest that even men who undergo early orchidopexy still harbour a higher risk of testicular cancer than men without cryptorchidism [74]. The management of adult cryptorchidism depends on hormone and spermatogenic evaluation results. For men with a normal functioning contralateral testis, orchidectomy of the undescended testicle may be offered owing to the higher risk of testicular cancer and germ cell neoplasia in situ (GCNIS) [75] (Table 5). In patients with a unilateral undescended testis and impaired testicular function of the contralateral testis as evidenced by biochemical hypogonadism and/or impaired sperm production (infertility), orchidopexy may be offered to preserve androgen production and fertility. However, according to consensus among the panel members, multiple biopsies of the unilateral undescended testis are recommended at the time of orchidopexy to exclude intratesticular GCNIS as a prognostic indicator of the future development of testicular germ cell tumour (TGCT). Moreover, at the time of orchidectomy for treatment of TGCT, biopsy of the contralateral testis should be offered to patients at high risk for GCNIS (history of cryptorchidism, testicular volume <12 ml, hypospermatogenesis) [76].

3.3.2. Germ cell malignancy and male infertility

TGCT is the most common malignancy among Caucasian men aged 15–40 yr and affects approximately 1% of subfer- tile men [77]. Infertile men are at higher risk of testicular cancer and other types of cancer [78]. Men with TGCT have lower semen quality, even before cancer treatment. Azoospermia has been observed in 24% of men with TGCT [79] and oligospermia in 50% [80]. Given that the average

Table 5 – Recommendations for specific male infertility conditions

Recommendation	Strength rating
Do not use hormonal treatment for cryptorchidism in postpubertal men.	Strong
Perform simultaneous testicular biopsy for detection of intratubular germ cell neoplasia in situ (formerly carcinoma in situ) if undescended testes are corrected in adulthood.	Strong
Offer orchidectomy to adult men with a unilateral undescended testis and normal hormonal function/spermatogenesis.	Strong
For adult men with a unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (ie, infertility), offer unilateral or bilateral orchidopexy if technically feasible.	Weak
Advise men with TM to perform self-examination even without additional risk factors, as this may result in early detection of TGCT.	Weak
Do not perform testicular biopsy, follow-up scrotal US, measure biochemical tumour markers, or abdominal or pelvic computed tomography in men with isolated TM without associated risk factors (eg, infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Offer testicular biopsy to infertile men with TM who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (<12 ml), history of undescended testes, and TGCT.	Weak
Perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after a multidisciplinary team meeting and discussion with the patient if there are suspicious findings on physical examination or US in patients with TM with associated lesions.	Strong
Manage men treated for TGCT in a multidisciplinary team setting with a dedicated late-effects clinic and survivorship programme, as they are at higher risk of developing hypogonadism, sexual dysfunction, and cardiovascular disease.	Strong
Perform sperm cryopreservation before planned orchidectomy or before additional neoadjuvant or adjuvant oncological therapies.	Strong
Offer onco-TESE at the time of radical orchidectomy in men with testicular cancer and azoospermia or severe abnormalities in their semen parameters.	Strong
For adolescents, offer surgery for varicocele associated with a persistent small testis (size difference of >2 ml or 20%), which should be confirmed on two subsequent visits performed 6 mo apart.	Strong
Do not treat varicocele in infertile men who have normal semen analysis or in men with a subclinical varicocele.	Strong
Treat infertile men with a clinical varicocele, abnormal semen parameters, and otherwise unexplained infertility in couples in which the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with elevated sperm DNA fragmentation with otherwise unexplained infertility and men with failure of assisted reproductive techniques, including recurrent pregnancy loss and failure of embryogenesis and implantation.	Weak
Treat male accessory-gland infections, as this may improve sperm quality, although it does not necessarily improve the probability of conception.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

TESE = testicular sperm extraction; TGCT = testicular germ cell tumour; TM = testicular microcalcification; US = ultrasound.

10-yr survival rate for testicular cancer is 98% and it is the most common cancer among men of reproductive potential, it is mandatory to include counselling regarding fertility preservation before commencing any gonadotoxic treatment [80,81]. All men with cancer must be offered sperm cryopreservation before the therapeutic use of gonadotoxic agents or ablative surgery that may impair spermatogenesis or ejaculation (chemotherapy, radiotherapy, or retroperitoneal surgery) [82,83]. All patients should be offered preservation of ejaculated semen as the most cost- effective strategy for fertility preservation, or of sperm extracted surgically in cases of severe oligozoospermia or azoospermia (onco-TESE). Since chemotherapy and radio- therapy are teratogenic, contraception must be used during and for at least 6 mo after completion of treatment [84]. Treatment of TGCT can result in additional impairment of semen quality [85] and an increase in sperm aneuploidy for up to 2 yr following gonadotoxic therapy [86]. Sper- matogenesis usually recovers 1–4 yr after chemotherapy. Chemotherapy is also associated with DNA damage and an increase in SDF [87]. However, sperm aneuploidy levels often decline to pretreatment levels 18–24 mo after treat- ment [86]. In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the con- tralateral testis [88]. The risk of hypogonadism is higher for survivors of testicular cancer, and serum testosterone levels should be evaluated during management for these patients [89]. However, this risk is greatest at 6–12 mo after treatment, which suggests that there may be some improvement in Leydig cell function after treatment. There- fore, it is reasonable to delay initiation of testosterone therapy until the patient shows continuous signs or symptoms of testosterone deficiency [90].

Microcalcification within the testicular parenchyma can be found in 0.6–9% of men referred for testicular US [91,92]. TM has also been observed in men with TGCT, cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter syndrome, hypogonadism, disorders of sex development, and varicocele [93]. TM in healthy, asymptomatic individuals is associated with a low risk of concurrent or long-term development of TGCT or GCNIS of unclassified type [94]. However, a meta-analysis revealed that for men with a history of subfertility, cryptorchidism, or a previous TGCT, TM presence increased the risk of a concurrent TGCT (risk ratio 8.5, 95% CI 4.5–16.1; p < 0.0001) [94]. A systematic review and meta-analysis of case-control studies indicated that TM presence is associated with a 13-fold higher odds of testicular cancer among infertile men (pooled OR 18.11, 95% CI 8.09–40.55; p < 0.0001) [55]. Therefore, the association between TM and TGCT is controversial and the challenge is to identify men at risk of harbouring GCNIS and developing TGCT. Men potentially at high risk of harbouring or developing GCNIS include those with infertility, atrophic testes, unde- scended testes, history of TGCT, and contralateral TM; it has been suggested that men with these risk factors could be offered testicular biopsy [95,96].

3.3.3. Varicocele

Varicocele is present in almost 15% of the normal male population, 25% of men with abnormal semen analysis, and 35–40% of men presenting with infertility [97–99]. Worsening

semen parameters are associated with higher varicocele grade and age [98,100]. The exact association between lower male fertility and varicocele is unknown. Higher scro- tal temperature, hypoxia, and reflux of toxic metabolites can cause testicular dysfunction and infertility because of increased overall survival and DNA damage [97,99].

Varicocele repair has been a subject of debate for several decades. However, recent meta-analyses have demonstrated that treatment of clinical varicocele was associated with improvements in semen parameters and rates of pregnancy and live births [101]. Improvements in semen parameters are usually observed after surgical correction in men with preoperative abnormal sperm quality [102–104]. Conversely, treatment of subclinical varicocele was not effective at increasing the chances of spontaneous pregnancy [105]. In addition, randomised studies that included mainly men with normal semen parameters revealed no benefit favour- ing treatment over observation. Varicocelectomy can also reverse sperm DNA damage and improve oxidative stress levels [97,99]. A further meta-analysis revealed that varicocelectomy may improve outcomes following ART in oligozoospermic men (OR 1.69, 95% CI 0.95–3.02) [106]. After varicocele repair, the average time to improvement in semen parameters is up to two spermatogenic cycles [107,108], with spontaneous pregnancy occurring between 6 and 12 mo after varicocelectomy [109,110].

Varicocelectomy may lead to the presence of sperm in the ejaculate for men with azoospermia [111]. Moreover, meta-analyses have revealed that treatment of clinical varicoceles improved surgical SR rates among patients with NOA, especially for those with a histological diagnosis of hypospermatogenesis [112]. However, the quality of the evidence available is low, and the risks and benefits of varicocele repair must be discussed fully with patients with NOA and a clinically significant varicocele before embarking on treatment intervention, particularly in couples with a female partner with limited ovarian reserve [112,113].

Varicocelectomy can improve sperm DNA integrity [114–117]. A systematic review and meta-analysis of data from 1070 infertile men with clinical varicocele showed that varicocelectomy was associated with a reduction in postoperative SDF (weighted mean difference [WMD] −7.23%, 95% CI −8.86% to − 5.59%) [118]. Improvements in DNA integrity were independent of the assay used (sperm chromatic structure assay vs terminal deoxynucleotidyl transferase–mediated dUTP-biotin nick-end labelling vs sperm chromatin dispersion) and the surgical technique performed. The estimated WMD was greater in studies with preoperative mean SFD $\geq$ 20% than in studies with SDF <20%, suggesting that varicocelectomy might be more beneficial in men with elevated baseline SDF [118]. The magnitude of the effect size increased as a function of the preoperative SDF level (coefficient 0.23, 95%CI 0.07–0.39).

There is now increasing evidence that varicocele treatment may reduce DNA fragmentation and improve ART outcomes [106,114]. As a consequence, there is an argument that clinical varicoceles should be treated in the context of failed ART and when the male partner has high SDF once other causes of infertility have been excluded [119]. However, there has been no cost/benefit analysis of the utility of varicocele treatment in this setting, with limited prospective data on the effects of varicocele repair on both SDF and pregnancy and live birth outcomes. Moreover, it is not clear whether varicocele treatment is beneficial in men with normal sperm parameters but abnormal SDF. Therefore, the panel recommends that infertile patients with clinical varicocele or abnormal semen parameters should be counselled regarding the potential benefits of varicocele repair. Outside this remit, infertile men with abnormal SDF can be offered varicocele treatment, but must be counselled regarding the limited evidence on the benefits of intervention for this indication alone. In terms of surgical techniques, the microsurgical approach was associated with the lowest complication and recurrence rates and the highest spontaneous pregnancy rates. However, the data are too limited to definitively suggest that one technique is superior over any other [114].

3.3.4. Male accessory-gland infections and infertility

According to WHO, urethritis, prostatitis, orchitis, and epididymitis are male accessory-gland infections [120]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [121]. A systematic review of the relationship between sexually transmitted infections and infertility was unable to identify a strong association between sexually transmitted infections and male infertility owing to the limited quality of the data reported [122].

In terms of diagnostic purposes, a peroxidase-positive white blood cell level of >106/ml of ejaculate (also known as leukocytospermia) indicates an inflammatory process. However, this threshold is only an indicator of inflamma- tion and may not be related to infection. Therefore, semen culture or polymerase chain reaction analysis should be performed for common urinary tract pathogens in all sus- pected cases of genitourinary tract infections. A concentra- tion of >103 CFU/ml for urinary tract pathogens in ejaculate is indicative of significant bacteriospermia [123].

A meta-analysis of case-control studies showed that leukocytospermia in men seeking consultation for couple subfertility was not associated with lower fertility at ART or altered semen quality in men without symptoms of gen- ital tract infections [124]. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms improves conception rates [125]. A meta-analysis investigating the relationship between Myco- plasma and Ureaplasma infections and male infertility revealed that Ureaplasma urealyticum and Myocoplasma hominis strains were associated with male infertility, but not Ureoplasma parvum and Mycoplasma genitalium strains [126]. There is also emerging evidence that human papillomavirus infection may be associated with male infertility, but there is a paucity of prospective studies validating these findings and it is unclear whether antiviral treatment improves fertility outcomes [127–130]. A recent case- control study also highlighted that treatment of asymp- tomatic Chlamydia infection may improve sperm parame- ters, but it is not clear whether it improves conception rates [131].

Only antibiotic therapy of chronic bacterial prostatitis (type II according to the National Institutes of Health classi-

fication) has provided symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [132], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [133,134]. In this context, RCTs incorporating appropriate cost/benefit analyses and pri- mary outcome measures for pregnancy and live birth rates are needed to evaluate the role of antibiotics and probiotics in the treatment of male infertility. Lastly, it is important to refer the sexual partners of patients with accessory sex- gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.

3.4. Male infertility management

3.4.1. Noninvasive management of male infertility

Lifestyle changes. Lifestyle changes, including weight loss [135,136], physical exercise [137], and smoking cessation [138], can all enhance sperm parameters and should be encouraged, as they may also improve the overall health of infertile men (Table 6). This is particularly important given the increasing evidence that infertile men are at higher risk of developing cardiometabolic disorders [139] and have higher cardiovascular and overall mortality [140] in comparison to fertile control subjects. Therefore, all infer- tile men should be screened for any modifiable risk factors for cardiovascular disease, and a urological assessment represents an opportunity to target occult, early-stage disease and potentially improve life expectancy.

Oxidativestresstherapy.Oxidativestressisconsidered to be an important contributing factor to idiopathic male infertility. As previously reported, high ROS levels in semen are associated with impaired sperm parameters, high SDF [141], and adverse ART outcomes [142]. Therefore, several studies have investigated the impact of empiric antioxidant therapy in male infertility. Overall, evidence for the role of antioxidant therapy in male infertility is still conflicting. A Cochrane systematic review and meta-analysis that included 61 studies involving 6264 infertile men aged 18–65 yr showed that antioxidant therapy may improve the live birth rate, but the quality of evidence was low, and when studies with high risk of bias were removed, an increase in the live birth rate was no longer apparent [143]. More recently, a systematic review and meta-analysis of 45 RCTs involving 4332 infertile patients showed that patients treated with antioxidants had significantly higher sperm concentration, sperm progressive motility, sperm total motility, and normal sperm morphology in comparison to a control group [141]. Moreover, the authors found significantly higher pregnancy rates for patients treated with antioxidants in comparison to placebo-treated or untreated control subjects. The major concern regarding antioxidant treatment is the lack of clear consensus in the literature on the optimal antioxidant constituents or regimen. Therefore, antioxidants can only be considered an empiric treatment until more large-scale RCTs are performed.

Prebioticandprobioticsupplements.Inrecentyears, prebiotic/probiotic supplementation has been investigated for male infertility. An RCT including 56 men with idiopathic infertility treated with a prebiotic/probiotic compound versus placebo showed a significant increase in sperm parameters in the treated group (sperm concentration, motility, and normal morphology) and an increase in DNA integrity [144]. However, further high-powered RCTs are warranted to further investigate the use of prebiotic/probiotic supplementation in this context.

Hormonaltreatment.Theuseofgonadotropinsin secondary hypogonadism is well established [145] and a meta-analysis revealed that use of hCG with or without FSH resulted in sperm production detected in the ejaculate of 75% of NOA patients with hypogonadotropic hypogonadism [146]. The use of hormone stimulation therapy in men with primary hypogonadism and eugonadal men with idiopathic male infertility remains controversial [147].

Selective oestrogen receptor modulators (SERMs) block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion and leads to an increase in pituitary gonadotropin release and potential stimulation of spermatogenesis [148]. A meta-analysis of

Table 6 – Recommendations for noninvasive management of male infertility

Recommendation	Strength rating
Inform infertile men about the detrimental effects of obesity, low physical activity, smoking, and high alcohol intake on sperm quality and testosterone levels. Therefore, advise infertile men to improve lifestyle factors to improve their chances of conception.	Strong
Do not routinely treat patients with idiopathic infertility with antioxidants, prebiotics/probiotics, selective oestrogen receptor modulators, or aromatase inhibitors.	Weak
Induce spermatogenesis in men with congenital or acquired hypogonadotropic hypogonadism who wish to conceive via effective drug therapy (hCG, human menopausal gonadotropins, recombinant FSH, highly purified FSH).	Strong
Use FSH treatment to increase spermatogenesis in men with idiopathic oligozoospermia and FSH values within the normal range.	Weak
Do not treat idiopathic infertility with high-dose FSH.	Weak
Do not start hormonal stimulation before TESE in men with NOA outside clinical trials.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong
Provide testosterone therapy for symptomatic patients with primary or secondary hypogonadism who are not considering parenthood.	Strong
Offer dopamine agonist therapy to men with proven hyperprolactinaemia to improve sperm quality.	Weak
Withdraw anabolic steroids in infertile men for 6–12 mo before considering treatment with selective oestrogen receptor modulators or gonadotrophin therapy to induce spermatogenesis.	Weak

FSH = follicle-stimulating hormone; NOA = nonobstructive azoospermia; TESE = testicular sperm extraction.

data from 11 RCTs showed that SERMs significantly increased pregnancy rates and sperm and hormonal param- eters [149]. Similar results were confirmed in the latest updated meta-analysis of 16 studies [148]. It should be recognised that the quality of the papers considered was low, and only a few studies were placebo-controlled; there- fore no conclusive recommendations can be drawn regard- ing SERM use in men with idiopathic infertility.

Aromatase inhibitors may decrease oestrogen production by reversibly inhibiting the cytochrome p450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex, which in turn inhibits the negative feedback of oestrogen on the hypothalamus, resulting in stronger GnRH pulses that stimulate the pituitary to increase FSH production [150–153]. In this context, it has been reported that aromatase inhibitors as an off-label option increase endogenous testosterone production and improve spermatogenesis in the infertility setting [154]. Both steroidal (testolactone) and nonsteroidal (anastrozole and letrozole) aromatase inhibitors significantly improve hormonal and semen parameters in infertile men, with a safe tolerability profile, although prospective RCTs are necessary to better define the efficacy of these agents in this clinical setting [152,154].

There is some evidence that FSH treatment increases sperm parameters in men with idiopathic oligozoospermia who have FSH levels within the normal range (generally 1.5–8 mIU/ml) [155]. FSH administration for men with idiopathic infertility has been evaluated in more than 20 clinical trials, as summarised in four different meta-analyses [156–158]. These studies collectively suggest that FSH administration significantly increases sperm production (in terms of sperm concentration and total sperm count) in a dose-dependent manner [159,160]. Moreover, this treatment significantly increased both spontaneous and ART pregnancy rates. No significant difference was observed between ICSI and intrauterine insemination [156]. It has also been reported that in addition to SDF, FSH may improve AMH and inhibin levels [161–164]. A few studies have also investigated the role of hormone stimulation before TESE in azoospermic men (Section 3.4.3). Overall, the evidence for FSH/hCG treatment is limited by the low number of studies and small cohort sizes, and no clinical recommendations can be made. Therefore, large-scale RCTs are needed before hormone stimulation therapy can be recommended in routine clinical practice for eugonadal men or men with NOA.

3.4.2. Invasive management of male infertility

3.4.2.1. Obstructive azoospermia.

OA, which accounts for 20–40% of all azoospermia cases, is the absence of sperm in the ejaculate secondary to a blockage in the conduit of sperm rather than an abnormality of spermatogenesis [120]. OA is classified according to the anatomic position of the obstruction (intratesticular, epididymal, vasal, ejacu- latory duct, or functional obstruction of the distal seminal ducts). From a clinical standpoint, OA is characterised by normal FSH values, testes of normal size, and low semen volume [165]. Other potential clinical features of OA include an enlarged and dilated epididymis, nodules in the epi- didymis or vas deferens, and absence of the vas in cases of CBAVD [166].

Management of OA depends on the cause and site of obstruction: intratesticular obstruction requires TESE, while men with epididymal obstruction or vasal obstruction at the inguinal level can be offered either microsurgical reconstruction (eg, vasoepididymostomy) or SR using microsurgical epididymal sperm aspiration, percutaneous epididymal sperm aspiration, or TESE [167] (Table 7). Overall, preg- nancy outcomes from ICSI in men with OA are comparable between epididymal and testicular sperm, and between fresh and frozen–thawed epididymal sperm [168]. Vas def- erens obstruction following vasectomy can be treated with vasectomy reversal, for which the microsurgical technique has a successful patency rate of 90–97% [167].

Ejaculatory duct obstruction secondary to postinflammatory or cystic obstruction can be treated with transurethral

Table 7 – Recommendations for the surgical management of male infertility

Recommendation	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by vasal or epididymal obstruction in men with female partners with good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration, TESE, and percutaneous techniques (PESA and TESA), either as an adjunct to reconstructive surgery or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong
Confirm diagnosis of NOA in two consecutive semen analyses when no spermare found after centrifugation.	Strong
Perform a comprehensive assessment, including a detailed medical history, hormonal profile, genetic tests, and scrotal ultrasound, to investigate the underlying aetiology and associated comorbidity in patients with NOA.	Strong
Genetic counselling is mandatory for couples with genetic abnormalities before any assisted reproductive technology.	Strong
Perform surgery for sperm retrieval in men who are candidates for assisted reproductive technology (ie, ICSI).	Strong
Do not perform surgery for sperm retrieval in patients with complete AZFa and AZFb microdeletions, since the chance of sperm retrieval is zero.	Strong
Do not perform FNA and TESA in patients with NOA.	Strong
Do not perform FNA mapping as a prognostic procedure before definitive testicular sperm extraction (any type) in patients with NOA	Weak
Use microdissection TESE as the treatment of choice to retrieve sperm in patients with NOA.	Weak
Do not consider preoperative biochemical and clinical variables as sufficient and reliable predictors of sperm retrieval outcome at surgery in patients with NOA.	Weak
Do not routinely use medical therapy (eg, hormonal stimulation) in men with NOA and hypergonadotrophic hypogonadism before conventional or microdissection TESE to improve sperm recovery.	Weak

FNA = fine needle aspiration; ICSI = intracytoplasmic sperm injection; NOA = nonobstructive azoospermia; PESA = percutaneous epididymal sperm aspiration; TESA = testicular sperm aspiration; TESE = testicular sperm extraction.

resection of the ejaculatory ducts (TURED). The pregnancy rate following TURED is 12.5–31% [169], but the patient must be counselled on potential complications, including epididymitis, failure, urinary incontinence, and urine reflux into the ejaculatory ducts and seminal vesicles. In all cases of OA for which surgical reconstruction is being considered, the ovarian reserve of the female partner must be taken into account when evaluating treatment options such as SR and ICSI.

3.4.2.2. Nonobstructiveazoospermia.NOAisdefinedasthe absence of sperm in the ejaculate after centrifugation. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal axis. NOA should be confirmed by at least two consecutives semen analyses after centrifugation [7]. Clinically, men with NOA usually have low testicular volume, normal sperm volume, and high FSH values.

Spermatogenesis within the testes may be focal, which means that spermatozoa can usually be found in small and isolated foci. With a wide variability among cohorts and techniques, positive SR after TESE has been reported in up to 50% of NOA patients [170,171]. Numerous predictive factors for positive SR have been investigated, although no definitive factors have accurately predicted positive SR [171]. The presence of hypospermatogenesis at testicular biopsy was associated with good accuracy in predicting positive SR after TESE in comparison to the maturation arrest pattern or SCOS [172–174]. Hormonal levels of FSH, LH, inhibin B, and AMH have been variably correlated with SR outcomes, but the data are from retrospective series and are limited [30,175–180]. Testicular volume as a predictor of positive SR has been inconsistent [172,175,179]. In case of complete AZFa and AZFb microdeletions, the likelihood of SR is almost zero and therefore TESE procedures are contraindicated [181].

Fine needle aspiration (FNA) mapping has been proposed as a prognostic procedure in selecting patients with NOA for TESE and ICSI [182]. FNA mapping may provide information on sites with a higher probability of retrieving sperm, and can thus serve as a guide for further SR surgery in the context of ART procedures such as ICSI. However, testicular mapping does not retrieve sperm and therefore two surgical procedures are needed when only one may be sufficient, which may delay treatment for infertile couples. Furthermore, no RCTs have compared mTESE with and without testicular mapping and there have been no studies that provided effective cost/benefit analyses. Therefore, the guidelines do not recommend testicular FNA mapping as a primary diagnostic procedure before TESE in men with NOA until further prospective comparative studies are undertaken.

3.4.2.3. ConventionalandmicrodissectionTESE.Conventional TESE (cTESE) involves performing random biopsies of the testicle to retrieve sperm, for which SR rates in single-arm studies are ~ 50% [170]. Observational studies have demonstrated that multiple biopsies yield a higher chance of SR [170,183]. cTESE has been associated with a higher rate of complications in comparison to other techniques [170]. Microdissection TESE (mTESE) uses operative microscopy to identify seminiferous tubules that are more likely to harbour sperm and mitigate inadvertent testicular vascular damage [184]. The rationale for this technique is to increase the probability of retrieving sperm with a lower amount of tissue sampled and a subsequent lower risk of complications. In a meta-analysis of males with NOA, mTESE resulted in successful extraction 1.5 times more often than cTESE [171]. However, another meta-analysis revealed that surgical SR rates were comparable between mTESE and cTESE [185]. Lower complication rates have been observed with mTESE than with cTESE for both hae- matoma and fibrosis [186]. Recovery of baseline testos- terone levels at long-term follow-up has been observed after both procedures [187,188]. It is also pertinent to note that data showing that salvage mTESE successfully retrieved sperm in 46.5% of patients with prior failed cTESE or testic- ular sperm aspiration [189].

The main limitation of the contemporary literature is the paucity of RCTs comparing cTESE and mTESE. Although there was no difference in SR rates between cTESE and mTESE for patients with NOA in the latest and most comprehensive meta-analysis [185], it is important to note that in all the individual trials comparing cTESE and mTESE, the latter was superior in retrieving sperm. Furthermore, the current data suggest that complications are less frequent after mTESE in comparison to cTESE, and therefore the consensus opinion of the panel is that mTESE is the optimum approach for surgical SR in NOA. However, this is based on low-quality evidence, and larger RCTs comparing SR rates, risks, and costs for mTESE versus cTESE are urgently needed.

3.4.3. Hormonal therapy before surgical SR approaches

It has been proposed that stimulation of spermatogenesis by optimising intratesticular testosterone can increase the chances of positive SR in men with NOA. Similarly, strate- gies to increase serum FSH levels could stimulate spermatogenesis. To this end, several treatment options are available, including hCG and/or FSH [163,190,191] and SERMs [192], but a standardised protocol is lacking. No RCT has shown a benefit of hormonal treatment in enhancing the chances of positive SR among patients with idiopathic NOA [147]. A meta-analysis has suggested that hormone stimulation before TESE might improve SR in eugonadal men, but not in patients with hypergonadotropic hypogonadism [193]; however, the studies included in the analysis had moderate or severe risk of bias, and randomised studies are needed to confirm these findings.

4. Conclusions

The present text represents a summary of the 2025 EAU guidelines on sexual and reproductive health pertaining to male infertility. In approximately 50% of infertile couples, a male factor can be identified; therefore, all infertile men should undergo an accurate assessment. Increasing data indicate that infertile men are at higher risk of nononcological and oncological comorbidities and must be screened

and counselled accordingly. Several empirical treatments are available for male infertility, but there is insufficient evi- dence to support their use in clinical practice. For more detailed information and a full list of references, refer to the full-text version of the guidelines on the EAU website.

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