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Review – Andrology

European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility

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Abstract

Context: The European Association of Urology (EAU) has updated its guidelines on sexual and reproductive health for 2021.
Objective: To present a summary of the 2021 version of the EAU guidelines on sexual and reproductive health, including advances and areas of controversy in male infertility.
Evidence acquisition: The panel performed a comprehensive literature review of novel data up to January 2021. The guidelines were updated and a strength rating for each recommendation was included that was based either on a systematic review of the literature or consensus opinion from the expert panel, where applicable.
Evidence synthesis: The male partner in infertile couples should undergo a comprehensive urological assessment to identify and treat any modifiable risk factors causing fertility impairment. Infertile men are at a higher risk of harbouring and developing other diseases including malignancy and cardiovascular disease and should be screened for potential modifiable risk factors, such as hypogonadism. Sperm DNA fragmentation testing has emerged as a novel biomarker that can identify infertile men and provide information on the outcomes from assisted reproductive techniques. The role of hormone stimulation therapy in hypergonadotropic hypogonadal or eugonadal patients is controversial and is not recommended outside of clinical trials. Furthermore, there is

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insufficient evidence to support the widespread use of other empirical treatments and surgical interventions in clinical practice (such as antioxidants and surgical sperm retrieval in men without azoospermia). There is low-quality evidence to support the routine use of testicular fine-needle mapping as an alternative diagnostic and predictive tool before testicular sperm extraction (TESE) in men with nonobstructive azoospermia (NOA), and either conventional or microdissection TESE remains the surgical modality of choice for men with NOA.

Conclusions: All infertile men should undergo a comprehensive urological assessment to identify and treat any modifiable risk factors. Increasing data indicate that infertile men are at higher risk of cardiovascular mortality and of developing cancers and should be screened and counselled accordingly. There is low-quality evidence supporting the use of empirical treatments and interventions currently used in clinical practice; the efficacy of these therapies needs to be validated in large-scale randomised controlled trials.

Patient summary: Approximately 50% of infertility will be due to problems with the male partner. Therefore, all infertile men should be assessed by a specialist with the expertise to not only help optimise their fertility but also because they are at higher risk of developing cardiovascular disease and cancer long term and therefore require appropriate counselling and management. There are many treatments and interventions for male infertility that have not been validated in high-quality studies and caution should be applied to their use in routine clinical practice.

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1. Introduction

Infertility is defined as the failure to achieve a spontaneous pregnancy despite 1 yr of practicing regular sexual intercourse without a contraceptive [1]. It has been reported that infertility affects 15% of all couples and contemporary evidence suggests that there has been a decline in global fertility rates from 4.7 to 2.4 live births between 1950 and 2017 [2]. In addition, there has been a parallel decline in sperm counts (0.70 million/ml/yr) observed between 1981 and 2013 [3].

There have been a number of technological advances in both the diagnostic and therapeutic management of male infertility, necessitating an update of the European Association of Urology (EAU) guidelines on male infertility [4]. The male infertility guidelines were first published in 2001 and last updated in 2018 [4]. There are several controversial aspects to the contemporary management of infertile males, confounded by a number of medical specialities that manage these patients, with no clear protocols and guidance on treatment options, resulting in variance in outcomes for patients.

2. Evidence acquisition

The panel performed a comprehensive literature review of novel data covering the time frame between 2018 and January 2021. Databases searched included Medline, EMBASE, and the Cochrane Libraries between 2018 and 2021 and restricted to English language publications.

A strength rating is provided for each recommendation according to the EAU Guideline Office methodology (modified from the Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodology) [5]. The full text on male sexual and reproductive health management can be found in the guidelines on the EAU website [6].

3. Evidence synthesis

3.1. Epidemiology and aetiology

The worldwide prevalence of infertility is 9% [7] and for 50% of infertile couples the cause is attributable to a male factor [8,9]. There are several recognised causes of impaired sperm parameters (Table 1), including the presence of varicoceles, hypogonadism, and genetic disorders.

Unexplained infertility is diagnosed when the male has normal semen parameters and his female partner has normal ovulation and fallopian tube patency [10] and has been reported to be the case for 15–30% of all infertile couples [11]. However there is increasing evidence suggesting that even men with normal sperm parameters can have underlying molecular abnormalities, such as increased sperm DNA fragmentation (SDF) [12–14] and elevated seminal reactive oxygen species (ROS) [14], which appear to confer to worse reproductive outcomes in couples [12,14–19]. Therefore, it is mandatory to assess both the male and female partners to investigate any potential underlying cause of their infertility and to treat any potential reversible factors [20].

3.2. Diagnostic workup

3.2.1. The role of molecular testing

Semen analysis performed according to World Health Organization (WHO) guidelines [21] is the gold standard investigation for male infertility. While a semen analysis can identify infertile males who will require surgical intervention (eg, azoospermia) from those who may conceive naturally, it has become evident that the WHO reference ranges for sperm count, motility, and morphology are poor discriminators between fertile and infertile men [22,23]. As a consequence, there has been an increasing focus on the development of diagnostic tests to assess the

biochemical and molecular functions of sperm, including measurement of seminal ROS [24] and SDF [25], which may be more predictive of fertility potential compared to standard semen parameters [26]. Furthermore, these biomarkers have been used to stratify patients who may experience success with assisted reproductive techniques (ART) [26–29].

Sperm DNA is highly organised and the degree of chromatin organisation can affect epididymal and embryo development [30]. The causes of abnormal SDF include male genital tract infections [31], smoking [32], oncological therapies (eg, chemotherapy) [33], and varicoceles [34]. It has been shown that an increase in SDF adversely affects the outcomes from both natural conception [35] and ART [36–38]. Moreover, abnormal SDF has been implicated as a contributory factor for both recurrent pregnancy loss [39–41] and unexplained infertility [12,14].

However, there are a number of different assays for measuring SDF and there is still no consensus on a reference assay or a threshold for normalcy or whether its measurement is cost-effective in the management of infertile couples, such as those undergoing ART [42,43]. The main advantage of performing SDF testing in clinical practice is that it allows the initiation of a urological assessment for men who would not otherwise be routinely reviewed by a urologist (eg, men from couples diagnosed with unexplained infertility or recurrent pregnancy loss who may have normal semen parameters and be presumed fertile). Hence, SDF testing in these groups of men may provide the opportunity to correct any reversible causes of SDF, including lifestyle changes, identification of accessory gland infections, and treatment of a varicocele (see Section 3.3.3 on varicocele) to optimise natural conception and improve ART outcomes [44–47].

Oxidative stress has also been implicated as a cause of male infertility. A careful balance between ROS and antioxidants is necessary for optimal sperm function, and excess seminal ROS results in oxidative stress leading to SDF and damage to the sperm plasma membrane [48,49]. Moreover, oxidative stress has been associated with impaired sperm motility, sperm count, and abnormal sperm morphology [50–52]. High levels of oxidative stress have been associated with abnormal SDF [53] and it has been purported that oxidative stress is one of the main pathophysiological mechanisms causing raised SDF [54–56]. Abnormal seminal ROS production has similar risk factors to those for SDF, including male genital tract infections [57], cigarette smoking [32,58], and the presence of a varicocele [59]. However, there is no standardised method of measuring seminal ROS, with a lack of prospective randomised controlled trials (RCTs) with appropriate cost-benefit analysis assessing its utility as a predictive biochemical marker for fertility outcomes. In this setting, the EAU guidelines panel for male sexual and reproductive health concluded that seminal ROS testing cannot be recommended in routine clinical practice until there is a validation of its diagnostic utility from further studies.

3.2.2. *Hormone testing*

Hypogonadism is classified as primary hypogonadism, which is caused by testicular pathology leading to impaired testosterone synthesis, or secondary hypogonadism, which results from insufficient gonadotropin stimulation of the testicles owing to a hypothalamic or pituitary defect [60]. Both primary and secondary hypogonadism can result in impaired sperm parameters or azoospermia [61,62]. Male infertility is associated with hypogonadism [63–65] and biochemical screening is recommended as part of the diagnostic work-up given its long-term sequelae for cardiometabolic health such as the metabolic syndrome (MetS) and higher cardiovascular risk [66].

While the use of hormone stimulation therapy in hypergonadotropic hypogonadism (see Section 3.4.1 on noninvasive treatments) is controversial, the treatment of hypogonadotropic hypogonadism can produce sperm in the ejaculate of men with nonobstructive azoospermia (NOA) and is established practice. The data on serum follicle-stimulating hormone (FSH) as a surrogate marker for spermatogenesis in men with NOA and thus the success of surgical sperm retrieval are conflicting [67,68] and therefore serum FSH cannot be used to predict the success of either conventional testicular sperm extraction (cTESE) or microdissection TESE (mTESE) or to preclude patients from undergoing surgical sperm retrieval [69].

3.2.3. *Genetic testing*

Genetic testing has become increasingly important in the management and counselling of infertile males. A pooled data analysis of 9766 infertile men with oligospermia or azoospermia revealed an incidence of chromosomal abnormalities of 5.8% [70]. The frequency of genetic anomalies appears to be related to the degree of spermatic dysfunction and it has been observed that NOA is associated with the highest prevalence of chromosomal abnormalities [71,72]. The precise sperm concentration threshold for initiation of genetic testing for infertile males remains controversial. The EAU guidelines advocate testing in patients with azoospermia and those with a sperm concentration of $<$10 million/ml. However, an external validation study [73] of the EAU threshold reported that this may have a low sensitivity and specificity and will still potentially miss 20% of infertile men with a karyotype abnormality. The EAU guidelines also recommend karyotype assessment if there is a family history of recurrent miscarriage, congenital malformations, or mental retardation, irrespective of the sperm concentration [4]. However, it must be appreciated that there is an absence of large-scale studies or data pertaining to the cost-effectiveness of karyotype testing in the context of its ability to predict ART failure, the miscarriage rate, and genetic abnormalities in offspring.

The most common sex chromosomal abnormality is Klinefelter syndrome, which has a variable clinical presentation ranging from a normal phenotype to clinical features of hypogonadism [74]. Similarly, the presence of germ cells or spermatogenesis is highly variable among men with Klinefelter syndrome, but it has been demonstrated that

surgery (cTESE or mTESE) can retrieve sperm in 50% of cases [67,75]. There is no consensus regarding the optimal age for surgical sperm retrieval in patients with Klinefelter syndrome and the contemporary literature is conflicting [76]. There are no studies reporting the sperm recovery rate in either ejaculate or from surgery in men with Klinefelter syndrome at different ages and thus it is unclear from the current evidence whether there is a decline in sperm recovery rates with age. Furthermore, it must be appreciated that Klinefelter syndrome diagnosed in childhood may represent a different clinical entity to Klinefelter syndrome diagnosed in adulthood, as children are typically diagnosed on the basis of phenotypic characteristics such as behavioural issues, while men in adulthood with Klinefelter syndrome often only present because of infertility [76]. Therefore, findings from fertility studies in children with Klinefelter syndrome may not be applicable to or representative of Klinefelter syndrome diagnosed in adulthood [76]. There are further conflicting data regarding whether age [68,77,78] and testosterone levels [68,77,78] are predictive of successful sperm retrieval in men with Klinefelter syndrome. Therefore, given the potential physical and emotional trauma of a surgical sperm procedure in adolescence, coupled with the uncertainties in the current literature, sperm retrieval in boys or adolescents as a fertility preservation treatment should not be performed routinely and must be considered experimental at this stage [76].

Outside the remit of fertility, men with Klinefelter syndrome are at higher risk of hypogonadism, thrombophilia, and metabolic (eg, diabetes and MetS), and cardiovascular diseases and malignancies (including haematological cancers, extragonadal germ cell tumours, and breast cancer) and therefore appropriate counselling and follow-up should be instigated [74,79,80].

Men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis) should have testing for mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Cystic fibrosis (CF) is the most common autosomal recessive disorder in the Caucasian population [81]. More than 1500 different *CFTR* gene mutations have been identified and *CFTR* mutations can be associated with congenital bilateral absence of the vas deferens (CBAVD) [82], for which a prevalence of approximately 2% among infertile men has been reported [82]. The clinical diagnosis of an absent vasa is easy to miss and all men with azoospermia should be carefully examined to exclude CBAVD, particularly those with a semen volume <1.0 ml and acidic pH <7.0. If an infertile male is diagnosed with *CFTR* mutations, it is mandatory to test the female partner because if she is a carrier then the risk of the child having CF is 50%. Moreover, the couple must be counselled appropriately because routine *CFTR* testing is limited to the most common mutations and even if the female partner tests negative there is an estimated 0.4% risk that she could be a carrier of a less common *CFTR* mutation [83].

Microdeletions on the Y chromosome (azoospermia factor A [*AZFa*], B [*AZFb*], and C [*AZFc*]) are common in NOA [84] and have important implications for both genetic counselling and surgical sperm retrieval rates. In addition, Y chromosome microdeletions are absent in men with normal sperm parameters and are rare in men with a sperm concentration >5 million/ml [84]. Therefore, the current EAU recommendations are that Y chromosome microdeletion testing can be offered to infertile men with a sperm concentration of <5 million/ml but should be considered mandatory for those with azoospermia or a sperm concentration ≤1 million/ml [4]. *AZFc* deletions are the most common (65–70%), followed by Y-chromosome deletions of the *AZFb, AZFb + AZFc*, and *AZFa + AZFb + AZFc* regions (25–30%). Deletions of the *AZFa* region are rare (5%). Complete deletion of the *AZFa* region is associated with Sertoli cell–only syndrome (SCOS), while complete deletion of the *AZFb* region is associated with spermatogenic arrest. It is pertinent to note that complete deletions of the *AZFa* and *AZFb* regions predict poor prognosis for surgical sperm retrieval and therefore TESE should not be attempted in these patients [84–86]. By contrast, deletions of the *AZFc* region may result in a variable clinical presentation that can include oligospermia or azoospermia [84] and the contemporary literature demonstrates that sperm can be successfully retrieved in 53–75% of men with an *AZFc* deletion [85,87,88]. However, it must be recognised that any male offspring conceived from a male with an *AZFc* deletion will inherit this genetic mutation and it is important that couples undergo genetic counselling before treatment.

3.2.4. *Imaging*

Scrotal ultrasound should be included in the diagnostic work-up for infertile males to exclude testicular neoplasms, as it has been reported that male infertility is an additional risk factor for testicular cancer [89,90], which is likely to be the result of testicular dysgenesis [91]. A retrospective cohort study of 20 433 patients observed that infertile men had a higher risk of testicular cancer in comparison to fertile men (hazard ratio [HR] 3.3, 95% confidence interval [CI] 1.6–6.9) [89]. The same study noted that oligospermic men had an approximately four times higher risk of developing testicular cancer in comparison to normospermic men (HR 3.8, 95% CI 1.6–8.7) [89]. Furthermore, a meta-analysis of eight studies revealed that the presence of testicular microlithiasis (TM) in infertile men significantly increased the risk of developing testicular cancer (pooled odds ratio [OR] 18.11, 95% CI 8.09–40.55; $p < 0.0001$) [90]. However, there have been no large-scale studies providing an appropriate cost-benefit analysis of the routine use of ultrasound screening for infertile men. Moreover, there are concerns that routine screening could result in overdiagnosis of incidental testicular masses, of which a significant proportion will be indeterminate and require further surveillance or intervention [92].

There are no definitive ultrasound size criteria to distinguish between benign and malignant testicular lesions, but there are limited data suggesting that a lesion size of <5 mm is more likely to be benign ($p = 0.002$) [93]. A further study reported that an ultrasound diameter threshold or cutoff value of 8.5 mm was able to discriminate

Table 1 – Recognised causes of impaired sperm parameters

Pathology	Example
Congenital urogenital abnormality	Cryptorchidism [113]
Acquired urogenital abnormality	Vasectomy
Malignancy	Testicular cancer [218]
Elevated scrotal temperature	Varicocele [219]
Endocrine dysfunction	Hypogonadotropic hypogonadism [62]
Genetic abnormalities	Klinefelter syndrome [75,220]
Immunological factors	Antisperm antibodies [221]

between benign and malignant lesions with sensitivity of 81% and specificity of 58% [94]. Other proposed ultrasonographic predictive factors for benign pathology include hyperechoic and nonvascular lesions on Doppler ultrasound [4,95–98]. Although histological diagnosis remains the gold standard in differentiating benign from malignant lesions, the majority of testicular lesions identified incidentally during work-up for infertility will be benign and thus testicular biopsy may be considered as overinvestigation [94,99]. Therefore, a multidisciplinary team (MDT) approach should be adopted, with consideration of risk stratification for malignancy, including interval growth of the lesion and ultrasound prognostic features (eg, size >5 mm, echogenicity, and vascularity of the lesion).

There are data advocating the use of ultrasound-guided intraoperative frozen section analysis [100] but this may not be universally available. However, ultrasound-guided intraoperative frozen section analysis and testis-sparing surgery with tumour enucleation can be considered as an alternative to radical orchidectomy in the management of indeterminate lesions after full patient counselling and MDT discussion. Irrespective of the choice of treatment, for men with azoospermia, synchronous mTESE may be performed as a fertility preservation procedure and systematic testicular biopsies will be able to exclude the presence of an associated intratubular germ cell neoplasia in situ (GCNIS), formerly known as carcinoma in situ of the testes.

In view of the association between infertility and testicular cancer, the EAU guidelines panel recommends counselling of infertile males regarding the need to perform regular testicular examinations.

While varicoceles are typically identified during physical examination, colour Doppler ultrasound can confirm the diagnosis and provide additional information on the presence of venous reflux and venous diameter to differentiate radiologically significant varicoceles (varicoceles with a venous diameter >3 mm in both the upright position and during the Valsalva manoeuvre, and a venous reflux duration of >2 s) [101,102].

Similarly, scrotal ultrasound has been used to demonstrate the presence or absence of the vas deferens, seminal vesicles, and epididymal abnormalities [103,104]. Transrectal ultrasound may be able to identify ejaculatory duct cysts, ejaculatory duct obstruction and dilatation, and atrophy or

Table 2 – Recommendations for the diagnostic work-up of male infertility[a]

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of infertile males, since this might determine decision-making in terms of timing and therapeutic strategies (eg, ART versus surgical intervention).	Strong
A complete medical history, physical examination, and semen analysis are the essential components of any male infertility evaluation.	Strong
Perform a full andrological assessment for all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa <10 million/ml) for diagnostic purposes.	Strong
Testing for Y-chromosome microdeletions may be offered to men with a sperm concentrations of <5 million/ml, but should be mandatory for men with a sperm concentration of ≤1 million/ml.	Strong
Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the *AZFa* and *AZFb* regions, since these are an indicator for poor prognosis for sperm retrieval at surgery.	Strong
Inform men with a Yq microdeletion and their partners who wish to proceed with ICSI that microdeletions will be passed to sons, but not to their daughters.	Strong
For men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for mutations of the cystic fibrosis transmembrane conductance regulator gene, which should include common point mutations and the 5T allele.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For men with Klinefelter Syndrome offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use ROS testing in the diagnosis and management of the male partner of an infertile couple.	Weak
SDF testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception or failed ART and for men with unexplained infertility.	Strong
Perform scrotal US in patients with infertility, as they have a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (eg, US-guided testis biopsy with frozen section vs radical orchidectomy vs surveillance) should be considered for infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak
Perform transrectal US if a partial or complete distal obstruction is suspected.	Strong

ART = assisted reproductive techniques; ICSI = intracytoplasmic sperm injection; ROS = reactive oxygen species; SDF = sperm DNA fragmentation; US = ultrasound.

[a] Amended table from the European Association of Urology guidelines on sexual and reproductive health [6].

hypoplasia of the seminal vesicles in men with azoospermia with low ejaculate volume [103,104].

Table 2 summarises the recommendations on diagnostic work-up for male infertility from the EAU guidelines [6].

3.3. Specific conditions

3.3.1. Cryptorchidism

It has been reported that cryptorchidism affects approximately 1% of all infants according to 1-yr assessment records [105]. The degeneration and decline of germ cells in cryptorchidism occur within the first year of life and therefore surgery has been advocated within 12 mo of birth to mitigate this risk [106], while early orchidopexy improves sperm counts [107–109] and reduces the risk of testicular cancer in adulthood [110]. The gold standard treatment for cryptorchidism is orchidopexy, and meta-analyses have revealed that hormone stimulation therapy as a primary treatment modality has poor success rates [111,112].

Paternity rates among men with a history of unilateral cryptorchidism are almost equivalent to those for men without cryptorchidism, but a background of bilateral cryptorchidism confers a paternity rate of 35–53% and men should be counselled accordingly [113]. Men with a background of cryptorchidism may also be at greater risk of hypogonadism [114] and therefore should be screened for hypogonadism, as men with hypogonadism have higher susceptibility to MetS, cardiovascular disease, and type 2 diabetes [66]. Furthermore, men with a history of cryptorchidism should also be counselled regarding their higher risk of testicular cancer and the need to practise regular self-examination [115].

The management of cryptorchidism diagnosed in adulthood is dependent on hormone and spermatogenic function. 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 GCNIS [116]. For men with unilateral cryptorchidism and a poorly functioning contralateral testis (eg, hypogonadism or impaired sperm function) or bilateral cryptorchidism, orchidopexy can be offered, but multiple testicular biopsies should be performed to exclude intratesticular GCNIS, which would confer a higher risk of future development of a germ cell tumour. More recently, a meta-analysis has shown that sperm may even appear in the ejaculate of men with bilateral cryptorchid testis after definitive orchidopexy [117].

3.3.2. Germ cell tumours

According to the testicular dysgenesis syndrome hypothesis, the rising incidence of testicular cancer, cryptorchidism, infertility, and hypospadias is due to in utero exposure to endocrine-disrupting chemicals [91]. Men with infertility are more likely to develop not only testicular but also other types of cancer [118,119]. Furthermore, men with testicular cancer are more likely to have abnormal semen parameters, with up to 24% and 50% of men presenting with NOA and oligozoospermia, respectively [120]. Therefore, all men undergoing potential gonadoablative treatments such as orchidectomy should receive fertility counselling with the option of sperm cryopreservation before orchidectomy. It has been observed that sperm cryopreservation is the most cost-effective method of fertility preservation for men with testicular cancer [121], but owing to resource availability this may not be feasible in some circumstances and orchidectomy should not be unduly delayed. For men undergoing orchidectomy who have azoospermia or severe oligospermia, a synchronous testicular sperm retrieval procedure (oncoTESE) should be performed [122].

While it has been demonstrated that gonadotoxic therapies such as chemotherapy can result in SDF and increases in sperm aneuploidy, reassuringly, these effects appear to be temporary and aneuploidy levels return to pretreatment levels 18–24 mo after treatment [123]. Moreover, studies have observed no increase in the risk of genetic abnormalities in the offspring of cancer survivors who had undergone chemotherapy or radiotherapy [124].

TM in healthy, asymptomatic individuals is associated with a low risk of concurrent or long-term development of testicular germ cell tumours or GCNIS of unclassified type [125]. However, a meta-analysis revealed that for men with a history of subfertility, cryptorchidism, or a previous testicular germ cell tumour, the presence of TM increased the risk of a concurrent testicular germ cell tumour (risk ratio 8.5, 95% CI 4.5–16.1; $p < 0.0001$) [125].

A further meta-analysis of eight studies including 150 infertile men with TM and 5088 infertile men without TM revealed that the presence of TM was associated with an approximately 18 times higher OR for testicular cancer (pooled OR 18.11, 95% CI 8.09–40.55; $p < 0.0001$) [90]. Therefore, some authors [126] have advocated a testicular biopsy for infertile patients with TM, but given the absence of large prospective cohort studies and the fact that most men with azoospermia will probably undergo a testicular biopsy to retrieve sperm (and histology can therefore be taken at this time), caution is warranted owing to the risk of overinvestigation in this patient population. However, all patients with TM should be counselled on the importance of regular testicular self-examination.

3.3.3. Varicocele

Varicoceles are present in 15% of the normal population and 35–40% of infertile men [127]. Meta-analyses have revealed that treatment of clinical varicoceles improves sperm parameters [128] and can potentially improve both pregnancy and live birth rates for oligospermic men, and pregnancy rates and sperm retrieval rates for men with NOA [46,47]. Furthermore, treatment of a clinical varicocele (grade 2/3) may facilitate sperm production in men with NOA [129,130] and meta-analyses have revealed that treatment of clinical varicoceles improved surgical sperm retrieval rates among patients with NOA, especially for those with a histological diagnosis of hypospermatogenesis [129,131]. However, the quality of evidence for performing varicocele treatment before surgical sperm retrieval is low and it must be recognised that the treatment could lead to potential delays in surgical sperm retrieval procedures and

Table 3 – European Association of Urology guideline recommendations for specific male infertility conditions[a]

Recommendation	Strength rating
Do not use hormonal treatment for cryptorchidism in postpubertal men.	Strong
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy for detection of intratubular germ cell neoplasia in situ (formerly carcinoma in situ).	Strong
Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (ie, infertility) may be offered unilateral or bilateral orchidopexy if technically feasible.	Weak
Men with TM should learn to perform self-examination even in the absence of additional risk factors, as this may result in early detection of TGCT.	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound, biochemical measurement of 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
Testicular biopsy may be offered to infertile men with TM in one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (<12 ml), history of undescended testes, or TGCT.	Weak
If there are suspicious findings on physical examination or ultrasound in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after a multidisciplinary team meeting and discussion with the patient.	Strong
Men treated for TGCT are at higher risk of developing hypogonadism, sexual dysfunction, and cardiovascular disease. Men should be managed in a multidisciplinary team setting with a dedicated late-effects clinic.	Weak
Sperm cryopreservation should be performed before planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak
Men with testis cancer and azoospermia or severe semen abnormalities may be offered oncotesticular sperm extraction at the time of radical orchidectomy.	Weak
Treat infertile men with a clinical varicocele, abnormal semen parameters, or otherwise unexplained infertility in a couple in which the female partner has a good ovarian reserve to improve the fertility rate.	Strong
Varicocelectomy may be considered in men with raised SDF with otherwise unexplained infertility or who have suffered from failed ART, including recurrent pregnancy loss or failure of embryogenesis and implantation.	Weak
MAGI treatment may improve sperm quality, although it does not necessarily improve the probability of conception.	Weak
The data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leucocytospermia will improve fertility outcomes.	Weak
Refer sexual partners of patients with a MAGI known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

ART = assisted reproductive techniques; MAGI = male accessory gland infection; SDF = sperm DNA fragmentation; TGCT = testicular germ cell tumour; TM = testicular microcalcification.
[a] Amended table from the European Association of Urology guidelines on sexual and reproductive health [6].

ART. A meta-analysis showed that treatment of clinical varicoceles in men with NOA may improve pregnancy rates but not live birth rates [47].

A Cochrane review revealed that treatment of varicoceles in the context of unexplained subfertility improved spontaneous pregnancy rates (OR 1.47, 95% CI 1.05–2.05; $p = 0.03$, $I^2 = 67\%$) but no study reported on live birth rates and the evidence was of low quality [45]. The authors also performed a subgroup analysis for only men with clinical varicoceles and abnormal sperm parameters, and observed that varicocele treatment was associated with an increase in the pregnancy rate (OR 2.39, 95% CI 1.56–3.66; $p = 0.03$; $I^2 = 64\%$).

A meta-analysis consisting of seven RCTs investigated the effects of varicocele treatment on spontaneous pregnancy rates for couples with unexplained infertility [132]. The authors observed that varicocele treatment did not significantly improve the pregnancy rate (OR 1.90, 95% CI 0.77–4.66; $p = 0.16$), but when the analysis was limited to clinical varicoceles and abnormal sperm parameters only (3 RCTs) there was a significant association favouring varicocele treatment (OR 4.15, 95% CI 2.31–7.45; $p < 0.001$).

A meta-analysis of seven studies involving 1241 men investigated the impact of varicocele repair treatment on ART. The authors observed that varicocele repair was associated with an increase in pregnancy rate for NOA men (OR 2.336; $p = 0.04$) and live birth rate for oligospermic men (OR 1.699; $p = 0.04$) [47]. A further meta-analysis specifically investigating intracytoplasmic sperm injection (ICSI) outcomes for NOA men with a clinical varicocele demonstrated that varicocelectomy was associated with an increase in both pregnancy (OR 1.59, 95% CI 1.19–2.12; $p = 0.002$; $I^2 = 25\%$) and live birth rates (OR 2.17, 95% CI 1.55–3.06; $p < 0.0001$; $I^2 = 0\%$) [46]. However, neither of the aforementioned meta-analyses included RCTs and both comprised of retrospective data.

There is also evidence that varicocele repair can improve SDF [133–136] and thus there is an argument that clinical varicoceles should be treated in the context of failed ART and where the male partner has a high SDF once other causes of infertility have been excluded [42]. 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 with abnormal SDF. Therefore, the EAU guidelines panel recommends that infertile patients with clinical varicoceles 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. Six

meta-analyses [137–142] have compared the different techniques for varicocele treatment. Overall, the microsurgical approach was associated with the lowest complication and recurrence rates and highest spontaneous pregnancy rates. However, the overall quality of evidence in these studies was low and further large-scale RCTs are needed to substantiate these findings. Moreover, it must be recognised that the microsurgical technique requires specialist microsurgical expertise, while radiological techniques are both minimally invasive and can be performed under local anaesthesia [143]. There are some data suggesting that robot-assisted varicocelectomy is comparable to the microsurgical approach [144,145], but further prospective randomised trials are needed to evaluate and validate this technique.

3.3.4. Male accessory gland infections

WHO categorises urethritis, orchiditis, prostatitis, and epididymitis as male accessory gland infections [1]. Contemporary data on the effects of symptomatic and asymptomatic infections and their treatment on sperm function are conflicting [146–149] and further well-designed studies are needed. A systematic review evaluating the association between sexually transmitted infections and male infertility observed that the current literature is contradictory, the evidence is of poor quality, and the data pertaining to potential pathophysiological mechanisms are limited [150].WHO defines leucocytospermia as $\geq 1 \times 10^6$ peroxidase-positive white blood cells/ml ejaculate and this is often used as a surrogate marker for potential infection [21]. However, this threshold is only an indicator of inflammation and may not be related to infection [151,152]. The current literature is conflicting with regards to whether antibiotics are effective in the treatment of infertile men with leucocytospermia and most of the studies have a high risk of bias [153]. Therefore, the WHO leucocytospermia threshold should be used to trigger a semen culture or polymerase chain reaction testing for common urogenital tract pathogens, for which a bacteria concentration of $\geq 10^3$ colony-forming units/ml is considered significant bacteriospermia [154]. A meta-analysis investigating the relationship between *Mycoplasma* 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 [155].

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 [156–159]. A recent case-control study also highlighted that treatment of asymptomatic *Chlamydia* infection may improve sperm parameters, but it is not clear whether it improves conception rates [160]. In this context, RCTs incorporating appropriate cost-benefit analyses and primary outcome measures of pregnancy and live birth rates are needed to evaluate the role of antibiotics and probiotics in the treatment of male infertility.

Epididymitis is a recognised cause of male infertility and can result in epididymal ductal stenosis and testicular atrophy, leading to both a reduction in sperm count and obstructive azoospermia (OA) or NOA. In sexually active men younger than 35 yr, epididymitis is more typically caused by *Chlamydia trachomatis* or *Neisseria gonorrhoea*, while in men who are not sexually active and those older than 35 yr, the cause is likely to be a urinary tract infection [161].

Table 3 details the EAU guideline recommendations for specific male infertility conditions.

3.4. Management of male infertility

The management of male infertility can be divided into noninvasive and invasive treatments.

3.4.1. Noninvasive treatments

Lifestyle modifications such as weight loss [162] physical exercise [163], and smoking cessation [164] all improve sperm parameters and should be recommended on the basis that they may improve the general health of the male partner. This is particularly relevant given the increasing evidence that infertile men are at higher risk of other comorbidities [165] and cardiovascular mortality [166] in comparison to fertile control subjects. Furthermore, there is a bidirectional relationship between MetS and hypogonadism [167] and both high alcohol intake and obesity are associated with hypogonadism, so efforts to change these lifestyle factors may increase testosterone levels [162,168]. Therefore, all infertile men should be screened for any modifiable cardiovascular disease risk factors, and a urological assessment represents an opportunity to target occult, early-stage disease and potentially improve life expectancy [66]. In addition, given the previously discussed association between male infertility and cancer, all men should be counselled regarding potential red flag signs and symptoms and should perform regular testicular self-examination.

The contemporary literature has reported an association between high seminal ROS levels and impaired sperm parameters [169], SDF [51,53], and adverse ART outcomes [15], and several studies have investigated the impact of empirical antioxidant therapy in male infertility. A Cochrane review of 61 studies showed that antioxidant therapy may improve the live birth rate, but the quality of evidence was low and when studies at high risk of bias were removed, an increase in the live birth rate was no longer apparent [170]. The authors also reported that antioxidant use may improve clinical pregnancy rates, but this was again based on low-quality evidence. Furthermore, there is no clear consensus in the literature on the optimal antioxidant constituents or regimen. Therefore, antioxidants can only be considered an empirical treatment until more large-scale RCTs are performed.

Intratesticular testosterone is required for spermiogenesis [171] and this has been the rationale for using hormone stimulation therapy as a treatment modality for male infertility. The use of gonadotropins in secondary hypogo-

Table 4 – European Association of Urology guideline recommendations for noninvasive treatments for male infertility[a]

Recommendation	Strength rating
For men with idiopathic oligoasthenoteratozoospermia, lifestyle changes, including weight loss, increased physical activity, smoking cessation, and a reduction in alcohol intake, can improve sperm quality and the chances of conception.	Weak
No clear recommendation can be made for the treatment of patients with idiopathic infertility using antioxidants, although antioxidant use may improve semen parameters.	Weak
No conclusive recommendations can be made regarding the use of selective oestrogen receptor modulators in men with idiopathic infertility.	Weak
No conclusive recommendations can be made regarding the use of either steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility, even before testis surgery.	Weak
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined hCG and FSH (recombinant FSH; highly purified FSH) or pulsed GnRH via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis with an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given regarding the use of high-dose FSH in men with idiopathic infertility before (microdissection) testicular sperm extraction and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin.
[a] Amended table from the European Association of Urology guidelines on sexual and reproductive health [6].

nadism is well established [172] and a meta-analysis revealed that the use of human chorionic gonadotropin with or without FSH resulted in the production of sperm in the ejaculate of 75% of NOA patients with hypogonadotropic hypogonadism [173].

The use of hormone stimulation therapy in men with primary hypogonadism or eugonadal men is more controversial [174]. Selective oestrogen receptor modulators [175,176], gonadotropins [177–179], and aromatase inhibitors [180] are commonly used to optimise sperm parameters in infertile men and as an adjunct to improve surgical sperm retrieval rates in men with NOA. However, there are no RCTs specifically analysing the benefits of hormone stimulation therapy in men with NOA and primary hypogonadism, and the literature consists of case-control studies with conflicting results [181–186]. Moreover, there is no consensus in the literature with regard to the most suitable hormone stimulation agent or regimen, and it should also be recognised that there are potential side effects associated with hormone stimulation therapy, including a paradoxical decline in serum testosterone and venous thromboembolism [174,185,187]. However, owing to the limited treatments available for this cohort of patients, especially those for whom surgical sperm retrieval surgery has failed, the use of hormone stimulation therapy is still common practice [174].

A Cochrane review suggested that the use of hormone stimulation therapy in oligospermic men may improve spontaneous pregnancy and live birth rates, but the evidence was limited by the low number of studies and small cohort sizes and no clinical recommendations could be made [178]. Therefore, large-scale RCTs are needed before hormone stimulation therapy can be recommended in routine clinical practice for eugonadal men or those with primary hypogonadism with oligozoospermia or NOA.

Table 4 details the EAU guideline recommendations for noninvasive treatments for male infertility.

3.4.2. *Surgical management*

3.4.2.1. Obstructive azoospermia. OA is the absence of sperm in the ejaculate secondary to a blockage in the conduit of sperm rather than an abnormality of spermatogenesis. It has been reported that OA contributes to 40% of all cases of azoospermia [188,189]. It is typically classified according to the anatomical position of the obstruction (intratesticular, epididymal, vasal, ejaculatory duct, or functional obstruction of the distal seminal ducts). Patients with OA often have a normal testicular size and hormone parameters, but men with NOA and the histological subtype of late maturation arrest can also have this clinical presentation [190]. Other potential clinical features of OA include an enlarged and dilated epididymis, nodules in the epididymis or vas deferens, and absence of the vas in cases of CBAVD [189,191]. Management of OA depends on the cause: intratesticular obstruction requires TESE, while men with epididymal obstruction or vasal obstruction at the inguinal level can be offered either microsurgical reconstruction (eg, vasoepidydostomy) or sperm retrieval using microsurgical epididymal sperm aspiration, percutaneous epididymal sperm aspiration, or TESE. Vas deferens obstruction following vasectomy can be treated with vasectomy reversal, for which the microsurgical technique has a successful patency rate of 90–97% [4,192,193]. Robot-assisted vasovasotomy has similar success rates to those for the microsurgical approach, but this may not be feasible in many institutions and the supporting literature is limited with respect to large prospective studies [194]. Ejaculatory duct obstruction secondary to postinflammatory or cystic obstruction can be treated with transurethral resection of the ejaculatory ducts (TURED). The pregnancy rate reported following TURED is 12.5–31% [195], but the patient must be counselled on potential complications, including epididymitis, failure, urinary incontinence, and urine reflux into the ejaculatory ducts and seminal vesicles [4,195]. The safety of TURED can be improved by intraoperative use of TRUS and

Table 5 – Recommendations for the surgical management of infertility[a]

Recommendation	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners with good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration, testicular sperm extraction, and percutaneous techniques, 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 a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong
Patients with NOA should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated comorbidities. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.	Strong
Surgery for sperm retrieval can be performed in men who are candidates for ART (ie, ICSI). For patients with complete *AZFa* and *AZFb* microdeletions, surgery is contraindicated since the chance of sperm retrieval is zero.	Strong
FNA and TESA should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to conventional TESE and microdissection TESE.	Weak
FNA as a prognostic procedure before definitive TESE (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Conventional or microdissection TESE is the technique of choice for retrieving sperm in patients with NOA.	Weak
No preoperative biochemical and clinical variables can be considered sufficient and reliable predictors of positive sperm retrieval at surgery for patients with NOA.	Weak
No conclusive recommendations can be made regarding routine use of medical therapy (eg, recombinant FSH; highly purified FSH; human chorionic gonadotropin; aromatase inhibitors or selective oestrogen receptor modulators) in patients with NOA before TESE.	Weak

ART = assisted reproductive techniques; FNA = fine needle aspiration; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; NOA = nonobstructive azoospermia; TESA = testicular sperm aspiration; TESE = testicular sperm extraction.

[a] Amended table from the European Association of Urology guidelines on sexual and reproductive health [6].

chemointubation of methylene blue into the seminal vesicles to confirm the patency of the ducts [4,195]. Alternatively, seminal vesiculoscopy and transurethral laser incision of the ejaculatory duct have been described as a treatment for ejaculatory duct obstruction [196]. However, in all cases of OA for which surgical reconstruction is being considered, the female partner's ovarian reserve must be taken into account when evaluating treatment options (eg, sperm retrieval and ICSI).

3.4.2.2. Nonobstructive azoospermia. cTESE involves performing random biopsies of the testicle to retrieve sperm. It has been reported that this approach yields an overall success rate of 35% for sperm retrieval [197]. mTESE utilises operative microscopy to identify seminiferous tubules that are more likely to harbour sperm and mitigate inadvertent testicular vascular damage. It has been reported that cTESE results in a greater volume of testicular tissue excised (9.4 vs 720 mg) [198] and a higher complication rate (haematoma formation and fibrosis) in comparison to mTESE. However, a recent meta-analysis reported that surgical sperm retrieval rates were comparable between mTESE and cTESE [68]. A further meta-analysis investigated the risk of hypogonadism following TESE (both cTESE and mTESE procedures) and observed that serum testosterone levels reduced at 3, 6, and 12 mo following these procedures, but returned to normal values by 18 mo [199]. It is also pertinent to note that data showing that a salvage mTESE successfully retrieved sperm in 46.5% of patients who had a prior failed cTESE or testicular sperm aspiration [200].

The predominant histological subtype in NOA has been utilised as a predictor of spermatogenesis. Hypospermatogenesis has higher rates of sperm retrieval compared to maturation arrest or SCOS histology [201–203]. However, even in SCOS there is at least a 24% chance of sperm retrieval and therefore histopathology should only be used to counsel men regarding the likelihood of finding sperm before a salvage sperm retrieval procedure [204,205]. The literature is inconsistent regarding the use of testicular size or hormone levels (eg, FSH) as predictors or surrogate markers of spermatogenesis and there do not appear to be any definitive predicative or prognostic clinical or biochemical factors for successful sperm retrieval in men with NOA [67,68,206–208].

Some authors have advocated the use of fine needle aspiration (FNA) sampling of the testicle before TESE [209]. This "testicular mapping" procedure has been advocated on the rationale that it allows assessment of the whole testicle and hence potentially reduces the risk of missing areas of isolated spermatogenesis. Moreover, testicular mapping may provide a targeted approach for subsequent TESE and thus theoretically reduces the degree of tissue excision and potential complications, although there are no data supporting this concept over standard TESE. Beliveau and Turek [210] observed a success rate of 90% for sperm retrieval using TESE in men who had more than two sites of spermatogenesis on FNA mapping. 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, there have been no RCTs comparing mTESE with and without testicular mapping or studies that have provided effective cost-benefit analyses. Therefore, the EAU guidelines do not advocate testicular FNA mapping as a primary diagnostic procedure before TESE in men with NOA until further prospective comparative trials are undertaken.

3.4.2.3. TESE for men without azoospermia. Several studies have investigated the use of testicular sperm compared to

ejaculate sperm for ART cycles because of the lower SDF [211], which may therefore lead to better pregnancy outcomes [211]. One meta-analysis compared SDF and ICSI outcomes between ejaculated and testicular sperm for men without azoospermia or cryptozoospermia [211]. The authors reported that testicular sperm had a lower SDF and higher fertilisation, clinical pregnancy, and live birth rates in comparison to ejaculated sperm. However, this meta-analysis was limited in that it only included five studies, the majority of which were observational, and there was no exclusion of confounding factors such as maternal age. In addition, there was significant heterogeneity in ovarian stimulation protocols and paternal ages. Therefore, the EAU guidelines advocate caution regarding the use of TESE for men without azoospermia given that the procedure exposes them to additional risks associated with surgery; furthermore, patients should be counselled on the low-quality evidence for this approach. Moreover, TESE should only be used in these circumstances once the other possible causes of high SDF have been comprehensively excluded.

Table 5 summarises the EAU guideline recommendations for the surgical management of infertility.

3.4.2.4. Assisted reproductive technologies. Several techniques have been developed to optimise sperm selection in the hope of improving ART outcomes, but meta-analyses have not supported the use of intracytoplasmic morphologically selected sperm injection (IMSI) [212] or physiological intracytoplasmic sperm injection [213]. A meta-analysis investigating the benefits of magnetic-activated cell sorting (MACS) [214] revealed that this technique may improve pregnancy rates (risk ratio 1.50, 95% CI 1.14–1.98; $p = 0.004$) but no differences were observed for miscarriage or implantation rates in comparison to the control group. However, this meta-analysis was limited by small study cohort sizes. There are some limited retrospective data [215] showing that MACS may improve ART outcomes for couples in which the man has high SDF, but these results need to be validated in RCTs.

Two meta-analyses [216,217] did not find any differences between ICSI and in vitro fertilisation (IVF) outcomes in terms of congenital malformations, but there is a paucity of data on older age groups and this should be a focus for future research.

4. Conclusions

The present text represents a summary of the 2021 EAU guidelines on sexual and reproductive health pertaining to male infertility. For approximately 50% of couples with infertility, the cause will be related to a male factor and therefore all infertile men should undergo urological assessment. Increasing data indicate that infertile men are at higher risk of nononcological and oncological comorbidities and must be screened and counselled accordingly. Currently, there is insufficient evidence to support the plethora of empirical treatments and interventions being used in clinical practice, and these therapies need to be validated in large-scale RCTs. For more detailed information and a full list of references, refer to the full-text version available on the EAU website (https://uroweb.org/guideline/sexual-and-reproductive-health/).

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