



## Guidelines

# European Association of Urology Guidelines on Male Infertility: The 2012 Update

Andreas Jungwirth<sup>a,\*</sup>, Aleksander Giwercman<sup>b</sup>, Herman Tournaye<sup>c</sup>, Thorsten Diemer<sup>d</sup>, Zsolt Kopa<sup>e</sup>, Gert Dohle<sup>f</sup>, Csilla Krausz<sup>g</sup>,  
EAU Working Group on Male Infertility

<sup>a</sup>EMCO Private Clinic, Bad Dürrenberg, Austria; <sup>b</sup>Reproductive Medicine Centre, Skane University Hospital, Lund University, Malmö, Sweden; <sup>c</sup>Centre for Reproductive Medicine, Free University of Brussels, Belgium; <sup>d</sup>Department of Urology, Paediatric Urology and Andrology, University Hospital Giessen and Marburg GmbH, Campus Giessen, Justus-Liebig-University, Giessen, Germany; <sup>e</sup>Andrology Centre, Department of Urology, Semmelweis University, Budapest, Hungary; <sup>f</sup>Erasmus University Medical Centre, Rotterdam, The Netherlands; <sup>g</sup>Sexual Medicine and Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy

### Article info

#### Article history:

Accepted April 24, 2012  
Published online ahead of print on May 2, 2012

#### Keywords:

Male infertility  
EAU guidelines  
Oligospermia  
Azoospermia  
Varicocele  
Hypogonadism  
Urogenital infection  
Genetic disorders  
Cryptorchidism

### Abstract

**Context:** New data regarding the diagnosis and treatment of male infertility have emerged and led to an update of the European Association of Urology (EAU) guidelines for Male Infertility.

**Objective:** To review the new EAU guidelines for Male Infertility.

**Evidence acquisition:** A comprehensive work-up of the literature obtained from Medline, the Cochrane Central Register of Systematic Reviews, and reference lists in publications and review articles was developed and screened by a group of urologists and andrologists appointed by the EAU Guidelines Committee. Previous recommendations based on the older literature on this subject were taken into account. Levels of evidence and grade of guideline recommendations were added, modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

**Evidence summary:** These EAU guidelines are a short comprehensive overview of the updated guidelines of male infertility as recently published by the EAU (<http://www.uroweb.org/guidelines/online-guidelines/>), and they are also available in the National Guideline Clearinghouse (<http://www.guideline.gov/>).

© 2012 European Association of Urology. Published by Elsevier B.V. All rights reserved.

\* Corresponding author. EMCO Private Clinic, Martin Hell Strasse 7-9, A-5422 Bad Dürrenberg, Austria. E-mail address: [andreas.jungwirth@utanet.at](mailto:andreas.jungwirth@utanet.at) (A. Jungwirth).

## 1. Definition

“Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year” (World Health Organisation [WHO], 2000) [1].

## 2. Epidemiology and aetiology

About 15% of couples do not achieve pregnancy within 1 yr; almost 50% of them do so spontaneously in the second year

of unprotected intercourse, and another 14% in the third year. Ultimately, <5% remain childless [2]. No cause of infertility can be found using routine diagnostic work-up in 10–15% of couples. A male contribution to infertility is found in 45–50% of the remaining cases [1]. In infertile couples, there is often a coincidence of male and female factors. Table 1 summarises the main factors associated with male infertility. In 30–45%, the cause of the abnormal semen parameters is not identified (idiopathic male infertility) [3,4].

**Table 1 – Male infertility causes and associated factors and percentage of distribution in 10 469 patients [3]**

Diagnosis	Unselected patients (n = 12 945) (%)	Azoospermic patients (n = 1446) (%)
All	100	11.2
Infertility of known (possible) cause	42.6	42.6
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Autoantibodies against sperm	3.9	–
Testicular tumour	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	<0.1	0.3
Others	0.8	0.8
Late-onset hypogonadism	2.2	–
Constitutional delay of puberty	1.4	–
General/systemic disease	2.2	0.5
Cryopreservation due to		
malignant disease	7.5	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
Disturbance of erection/ejaculation	2.4	–
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CBAVD)	0.5	3.1
Others	0.8	1.9
Gynecomastia	1.5	0.2
Y-chromosomal deletion	0.3	1.6*
Other chromosomal aberrations	0.2	1.3

CBAVD = congenital bilateral absence of vas deferens.  
\* This frequency refers to all azoospermic men (also including “nonidiopathic” cases).

### 3. Prognostic factors

The following main factors influence the prognosis in infertility:

- Age and fertility status of the female partner
- Duration of infertility
- Primary or secondary infertility
- Results of semen analysis.

Female age and associated decline in ovarian reserve is the most important single variable influencing outcome in both spontaneous and assisted reproduction [2]. Compared with a 25-yr-old woman, the fertility potential is reduced to 50% at 35 yr, to 25% by 38 yr, and <5% at >40 yr [5].

### 4. Medical history and physical examination

Investigation of the male partner should include a full medical history and physical examination according to the

standardised scheme published by WHO [1], so that any factor associated with male infertility can be diagnosed and treated if possible.

## 5. Investigations

### 5.1. Semen analysis

Semen analysis should follow the WHO guidelines, Laboratory Manual for the Examination and Processing of Human Semen [6]. Semen analysis may show a decreased number of spermatozoa (oligozoospermia), decreased motility (asthenozoospermia), and many abnormal forms on morphologic examination (teratozoospermia). These abnormalities usually come together and are described as the OAT syndrome (oligo-astheno-teratozoospermia). Seminal volume and pH can hint about conditions such as agenesis of seminal vesicles and vasa deferentia. Semen analysis in general is a poor predictor of pregnancy. Sperm DNA integrity assessment, by means of sperm chromatin structure assay, seems to be a valuable indicator of spontaneous pregnancy [7].

### 5.2. Hormonal investigation

Hypogonadotropic hypogonadism is a rare primary cause of male infertility. Hormonal screening can be limited to determination of follicle-stimulating hormone (FSH), luteinising hormone (LH), and testosterone levels, and it should be performed in all infertile men and in conditions with an increased risk of hypogonadism. In azoospermia, it is important to distinguish between obstructive and nonobstructive causes. A criterion with reasonable predictive value for obstruction is a normal FSH level with bilaterally normal testicular volume. However, 29% of men with normal FSH appear to have defective spermatogenesis (spermatogenic arrest) [8].

### 5.3. Microbiologic assessment

Indications for microbiologic assessment include abnormal urine samples, urinary tract infections, prostatitis, epididymitis, male accessory gland infection (MAGI), and sexually transmitted diseases [9]. In general, microbiologic assessment plays a minor role in diagnosing male infertility. Also, the clinical implications of detecting white blood cells in semen samples are as yet undetermined. However, in combination with a small ejaculate volume, this may point to a (partial) obstruction of the ejaculatory ducts caused by (chronic) infection of the prostate or seminal vesicles [9].

### 5.4. Ultrasonography

Scrotal ultrasound is mandatory for the assessment of testicular size; finding signs of obstruction, such as dilatation of the rete testis, enlarged epididymis with cystic lesions, absence of the vas deferens; and assessment of blood reflux in men with varicocele [10]. Scrotal ultrasound may also detect testicular microlithiasis (TM) in infertile men, which might indicate testicular carcinoma in situ (CIS).

In men with TM and associated risk factors for testicular cancer, such as testicular atrophy, history of cryptorchidism, low sperm counts, bilateral TM, and a history of contralateral cancer [10], the presence of TM should lead to the recommendation of a two-sided testicular biopsy for early detection of CIS.

Transrectal ultrasound (TRUS) of the prostate and seminal vesicles can be performed in patients with a low seminal volume and in whom distal obstruction is suspected such as seminal vesicle enlargement, midline prostatic cysts, and ejaculatory duct calcification associated with ejaculatory duct obstruction [11].

### 5.5. Testicular biopsy

Testicular biopsies can be performed for diagnostic and therapeutic reasons. Testicular spermatozoa can successfully be used for intracytoplasmic sperm injection (ICSI); therefore, it is strongly recommended to perform cryopreservation of testicular tissue (testicular sperm extraction [TESE]) for future ICSI, if spermatozoa are available [12]. A diagnostic testicular biopsy may be performed in men with azoospermia, normal testicular volume, and normal reproductive hormones to differentiate between obstructive azoospermia (OA) and nonobstructive azoospermia (NOA) and also for the diagnosis of CIS as described earlier [10,13].

## 6. Testicular dysfunction/nonobstructive azoospermia

Testicular dysfunction is the most frequent cause of disturbed spermatogenesis. Table 2 summarises the main causes of testicular dysfunction. Severe forms of testicular failure have a clinical presentation as severe OAT syndrome or NOA.

Typical findings from the physical examination of a patient with spermatogenic failure may be low testicular volume (<15 ml per testis) and/or consistency. FSH is often elevated (hypergonadotrophic hypogonadism); serum testosterone is within the normal range or at low levels [1]. In some cases, even abnormal secondary sexual characteristics and/or gynaecomastia may be seen.

**Table 2 – Classification and aetiologic factors of testicular failure**

Congenital factors	Anorchia
	Testicular dysgenesis/cryptorchidism
	Genetic abnormalities (karyotype, Y chromosome deletions)
Acquired factors	Testicular tumour
	Trauma
	Testicular torsion
	Postinflammatory forms (particularly mumps orchitis)
	Exogenous factors (medications, cytotoxic drugs, irradiation, heat)
	Systemic diseases (liver cirrhosis, renal failure)
	Varicocele
Idiopathic forms	Surgery that may compromise vascularisation of the testes and subsequently cause testicular atrophy
	Unknown pathogenesis

**Table 3 – Classification and aetiological factors of obstructive azoospermia**

Congenital forms	Epididymal dysjunction
	Congenital epididymal obstruction/agenesis
	Congenital bilateral or unilateral absence of the vas deferens
	Ejaculatory duct obstruction, Müllerian/utricular cysts
Acquired forms	Young syndrome (sinusitis, azoospermia syndrome)
	Intratesticular (rete testis) obstruction (infection)
	Epididymal obstruction (infection, previous surgery)
	Vas deferens obstruction (infection, vasectomy, hernia repair)
	Ejaculatory duct obstruction (infection, transurethral resection)

## 7. Obstructive azoospermia

OA is the absence of both spermatozoa and spermatogenic cells in semen and postejaculate urine due to the bilateral obstruction of the epididymis or the seminal or ejaculatory ducts (Table 3). Obstruction of the seminal tract should be suspected in patients with azoospermia or severe oligozoospermia with normal-size testes and normal FSH [1].

### 7.1. Classification

Intratesticular obstruction has been reported in 15% of patients with OA [14] and is usually caused by postinflammatory obstruction of the rete testis. Epididymal obstruction is the most common cause of OA [15]. Among the acquired forms, those secondary to epididymal infection are considered to be the most frequent [16].

Vas deferens obstruction following vasectomy is the most frequent cause of acquired obstruction. Approximately 2–6% of these men request vasectomy reversal [17]. Congenital bilateral absence of vas deferens (CBAVD) is found in 1 in 1600 men and in most men with cystic fibrosis (CF). Men with CBAVD appear to have mutations of the CF gene in at least 85% of cases. CBAVD can therefore be considered a mild genital form of CF [18]. Young syndrome, also referred to as sinusitis-infertility syndrome, is a rare combination of syndromes such as bronchiectasis, rhinosinusitis, and azoospermia because of functional obstruction of sperm transport down the genital tract [19]. Ejaculatory duct obstruction is found in 1–3% of cases of OA [20]. These obstructions can be classified as cystic or postinflammatory. Cystic obstructions are usually congenital (Müllerian duct cyst or urogenital sinus/utricular cysts) and are located medially in the prostate between the ejaculatory ducts [21]. Postinflammatory obstruction of the ejaculatory duct is usually secondary to urethral prostatitis. Congenital or acquired complete obstructions of the ejaculatory ducts or of the seminal vesicles are commonly associated with low semen volume, decreased or absent seminal fructose, and acid pH of seminal fluid. Typical clinical findings in men with OA may be normal testicular volume (>15 ml per testis), enlarged and indurated epididymis, nodules in the epididymis or vas deferens, absence or partial atresia of the vas deferens,

signs of urethritis or prostatitis, and prostatic abnormalities on rectal examination (palpation and/or TRUS).

## 8. Genetic disorders in infertility

### 8.1. Chromosomal abnormalities

In a survey of pooled data from 11 publications, including a total of 9766 infertile men, the incidence of chromosomal abnormalities was found to be 5.8%. Among these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities in pooled data from three series totalling 94 465 newborn male infants was only 0.38%, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) were autosomal abnormalities [22]. The risk of karyotype abnormalities increases with the severity of spermatogenic impairment. Patients with <10 million spermatozoa per millilitre show a 10 times higher incidence (4%) of mainly autosomal structural abnormalities compared with that in the general population. Men with primary testicular failure are at highest risk [23].

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is indicated in men with azoospermia or oligozoospermia with <10 million spermatozoa per millilitre [24]. In the case of a family history of recurrent abortions, malformations, or mental retardation, karyotype analysis should be requested regardless of the sperm concentration.

Klinefelter syndrome is the most frequent sex chromosome abnormality in men. The phenotype can vary from a normally virilised man to one with the stigmata of androgen deficiency, including female hair distribution, scanty body hair, and long arms and legs because of late epiphyseal closure [25]. However, all men with Klinefelter syndrome have small firm testes, and Leydig cell function is commonly impaired. Testosterone levels may be normal or low, oestradiol levels normal or elevated, and FSH levels are increased. Androgen replacement is often required with ageing. Spermatogenesis is frequently impaired and appears to deteriorate further after puberty. Most patients affected by this syndrome have azoospermia. However, TESE and especially microsurgical TESE, yields an average of a 30–50% testicular sperm recovery rate and may allow Klinefelter patients to generate their own genetic children through ICSI [26]. According to recent reviews, children born from Klinefelter fathers are healthy, and only one 47,XXY foetus has been reported so far [25]. As a result of the significant increase in sex chromosomal and autosomal abnormalities in the embryos of Klinefelter patients, ICSI and preimplantation genetic diagnosis should be considered an appropriate preventive option [27].

### 8.2. Y chromosome microdeletions

The long arm of the human Y chromosome (Yq) hosts several genes involved in spermatogenesis and several types of recurrent Yq deletions, called AZF deletions, which

are firmly associated with spermatogenic failure. AZF deletions are divided into AZFa, AZFb, and AZFc regions [28,29] and represent the most frequent molecular genetic cause of azoospermia and severe oligozoospermia. The clinical significance of AZF deletions can be summarised:

- Classical AZF deletions are never found in normozoospermic men and thus have a clear-cut cause-and-effect relationship with spermatogenic failure [30].
- The highest frequency is found in men with azoospermia (8–12%) followed by those with oligozoospermia (3–7%).
- Deletions are extremely rare with a sperm concentration >5 million/ml (about 0.7%).
- The most frequently deleted region is AZFc (65–70%), followed by deletions of the AZFb and AZFb+c or AZFa+b+c regions (25–30%), whereas deletions of the AZFa region are extremely rare (5%).
- Complete removal of the AZFa and AZFb regions is associated with severe testicular phenotype, Sertoli cell-only syndrome, and spermatogenic arrest, respectively.
- Complete removal of the AZFc region causes a variable phenotype that may range from azoospermia to oligozoospermia.

The specificity and the genotype/phenotype correlation just reported means that Y deletion analysis has both a diagnostic and a prognostic value for testicular sperm retrieval [31].

Yq microdeletion screening is indicated in all infertile patients with <5 million spermatozoa per millilitre [31]. Y deletions compatible with the presence of spermatozoa in the testis or ejaculate are obligatorily transmitted to the male offspring; therefore genetic counselling is mandatory. The extent of spermatogenic failure in male offspring may vary substantially; however, given the strict cause-and-effect relationship between AZF deletions and impaired spermatogenesis, normal spermatogenesis cannot be expected. A few cases of transmitted AZFc deletions have been reported; therefore, it is advised to extend the analysis to the male relatives of AZFc deletion carriers to ascertain the de novo nature of the deletion [31]. A novel type of AZFc deletion, called gr/gr deletion, was demonstrated by four recent meta-analyses as a significant risk factor for impaired sperm production. The frequency and the pathologic effect of this type of deletion vary in different ethnic groups, thus requiring cautious interpretation of the results [32].

### 8.3. Cystic fibrosis mutations and male infertility

CF is an autosomal-recessive disorder and the most common genetic disease of whites. Men with CF are azoospermic due to CBAVD. Isolated CBAVD is considered a mild form of CF, and so >80% of patients carry mutations of the CF transmembrane conductance regulator (CFTR) gene. This gene is located on the short arm of chromosome 7 and encodes a membrane protein that functions as an ion channel and also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens, and distal two-thirds of the epididymis (Wolffian duct structures) [31].

All men with CBAVD should be screened for *CFTR* mutation, with the exception of those who present with renal agenesis/malformation, which is probably related to another as yet unidentified gene defect [33]. The carrier frequency of *CFTR* mutations in persons of European descent is high (1:25); therefore, the female partners of men with CBAVD without congenital kidney anomalies or with CF should be screened for CF gene mutations before assisted reproduction. If mutations are detected in both partners, the risk of offspring with CF is high. However, it remains difficult in most cases to make precise risk estimates due to different degrees of penetrance of the same genotype between different individuals.

## 9. Varicocele

Varicocele is a common abnormality with the following andrologic implications:

- Failure of ipsilateral testicular growth and development
- Symptoms of pain and discomfort
- Reduced fertility.

### 9.1. Classification

The following classification of varicocele [1] is useful in clinical practice:

- Subclinical: Not palpable or visible at rest or during Valsalva manoeuvre but demonstrable by scrotal ultrasound and colour Doppler examination
- Grade 1: Palpable during Valsalva manoeuvre but not otherwise
- Grade 2: Palpable at rest but not visible
- Grade 3: Visible and palpable at rest.

### 9.2. Varicocele and fertility

Varicocele is a physical abnormality present in 11.7% of men with normal semen analysis and in 25.4% of men with abnormal semen [34]. The exact association between reduced male fertility and varicocele is unknown, but a meta-analysis showed that semen improvement is usually observed after surgical correction [35]. Current information fits with the hypothesis that in some men the presence of varicocele is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility. Varicocele is associated with increased sperm DNA damage, and this sperm pathology may be secondary to varicocele-mediated oxidative stress. Varicolectomy can reverse this sperm DNA damage, as shown in several studies [36].

### 9.3. Varicolectomy

Varicocele repair has been a subject of debate for several decades. Controversy exists about whether varicocele repair results in more spontaneous pregnancies as compared with observation. The 2009 Cochrane Database System Review

came to the conclusion that there is no evidence that treatment of varicocele improves a couple's chance of conception [37]. This meta-analysis has been criticised for including several heterogeneous studies of men with normal semen analysis and those with subclinical varicocele [38]. In three randomised controlled studies (RCTs), varicocele repair in men with subclinical disease was found to be ineffective [39–41]. Also, studies of men with varicocele and normal semen analysis have shown no clear benefit of treatment over observation [42,43].

The duration of infertility also seems of importance. A recent study showed that couples with an infertility duration >2 yr had a significant higher pregnancy rate compared with couples with uncorrected varicocele, but for couples with a shorter duration of infertility, such a difference was not observed [44].

In a recent meta-analysis of four RCTs of varicolectomy in men with clinical varicocele, oligozoospermia, and otherwise unexplained infertility, a trend in favour of surgical correction was observed [45]. The combined odds ratio was 2.23 (95% confidence interval [CI], 0.86–5.78;  $p = 0.091$ ), indicating that varicolectomy is moderately superior to observation, but the effect was not statistically significant.

Although treatment of varicocele in infertile men may be effective, in adolescents there is a significant risk of overtreatment. Most adolescents with a varicocele will have no problem achieving pregnancy later in life [46].

## 10. Hypogonadotrophic hypogonadism

Hypogonadotrophic hypogonadism is caused by either hypothalamic or pituitary diseases and can be congenital or acquired. Idiopathic hypogonadotrophic hypogonadism may be an isolated condition or associated with anosmia/hyposmia (Kallmann syndrome). Several genetic factors causing congenital deficit of gonadotrophins (LH or FSH) have been identified; however, the aetiology remains unknown in 70% of cases [47,48]. The diagnosis of congenital hypogonadotrophic hypogonadism is normally made before adulthood because in most boys it is associated with delayed puberty. However, in some patients, impaired spermatogenesis and mild hypoandrogenism may be the only symptoms, and thus the diagnosis may be delayed until adulthood [49]. Acquired hypogonadotrophic hypogonadism can be caused by a series of factors acting on the hypothalamus or at the pituitary level (Table 4).

**Table 4 – Classification of hypogonadotrophic hypogonadism**

Congenital forms	Kallmann syndrome Idiopathic hypogonadotrophic hypogonadism
Acquired forms	Tumours of the hypothalamus and pituitary gland Granulomatous disease Empty sella syndrome Haemochromatosis Obesity Anabolic steroids Age

The clinical picture depends on the aetiology. In most cases, gonadotrophin deficiency is accompanied by another deficit or an excess (in case of prolactinoma or acromegaly) of pituitary hormones.

## 11. Cryptorchidism and testicular tumours

Cryptorchidism is the most frequent congenital abnormality of the male genitalia, with a 2–5% incidence at birth. At 3 mo of age, the incidence is reduced spontaneously to 1–2%. The aetiology of cryptorchidism is multifactorial, and both disrupted endocrine regulation and several gene defects may be involved. For a normal descent of the testes, a normal hypothalamic-pituitary-gonadal axis is needed. Although most boys with maldescended testes show no endocrine abnormalities after birth, endocrine disruption in early pregnancy can potentially affect gonadal development and normal testicular descent. It has been postulated that cryptorchidism can be the consequence of testicular dysgenesis, a developmental disorder of the gonads due to environmental and/or genetic influences early in pregnancy. This testicular dysgenesis syndrome can result in maldescended testes, reduced fertility, hypospadias, and an increased risk for malignancy [50].

### 11.1. Relationship with fertility

Semen parameters in men with a history of cryptorchidism are often impaired. In 2–9% of infertile patients, a history of cryptorchidism is present. It has been suggested that surgical treatment performed at <3 yr of age has a positive effect on semen quality [51]. However, paternity in men with a history of unilateral cryptorchidism is almost equal (89.7%) to paternity in men without cryptorchidism (93.7%). Also, in men with unilateral cryptorchidism, paternity seems independent of age at orchidopexy, preoperative testicular location, and testicular size [52]. In men with bilateral cryptorchidism, however, oligozoospermia can be found in 31% and azoospermia in 42% of cases. In men with bilateral cryptorchidism, paternity is only 35–53% [53].

### 11.2. Germ cell tumours

Cryptorchidism is a risk factor for testicular cancer development and associated with TM and testicular CIS. In 5–10% of testicular cancers, a history of cryptorchidism can be found [54]. The risk of a germ cell tumour is higher in men with cryptorchidism and impaired fertility: 2–6% of men with a history of cryptorchidism and 0.5–1% of infertile men develop a testicular tumour.

### 11.3. Testicular microlithiasis

Microcalcification inside the testicular parenchyma can be found in 0.6–9% of men referred for testicular ultrasound [55]. Although the true incidence in the general population is unknown, it probably is a rare condition. However, the ultrasound findings are prevalent in men with germ cell tumours, cryptorchidism, testicular dysgenesis, male

infertility, testicular torsion and atrophy, Klinefelter syndrome, hypogonadism, male pseudohermaphroditism, varicocele, epididymal cysts, pulmonary microlithiasis, and non-Hodgkin lymphoma. The incidence seems to increase with the use of high-frequency ultrasound machines.

The relationship between TM and infertility is unclear, but it may be related to testicular dysgenesis, with slough of degenerated cells inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Secondly, calcification occurs [56].

TM is found in testes at risk for malignant development. The reported incidence of TM in men with germ cell malignancy is 6–46%. This has resulted in the hypothesis that TM should be considered a premalignant condition. It remains to be established, however, whether TM is present before the development of the invasive testicular germ cell tumours (TGCTs) and is therefore a putative parameter for the preinvasive stage of TGCTs, known as CIS. In testicular biopsies in men with TM, CIS is more prevalent, especially in those with bilateral microlithiasis and in the case of an inhomogeneous parenchyma on ultrasound [56]. In men with TM and a history of male infertility, cryptorchidism, or testicular cancer, and in those with testicular atrophy, testicular biopsy is recommended along with a follow-up scrotal ultrasound. It is also important to encourage and educate patients about self-examination because it may result in early detection of TGCTs. The routine use of biochemical tumour markers, abdominal and pelvic computed tomography, or testicular biopsy does not seem to be justified for patients with isolated TM.

## 12. Male accessory gland infection

Infections of the male accessory glands are potentially correctable causes of male infertility [57]. In this context, urethritis, prostatitis, orchitis, and epididymitis have been mentioned as MAGI by the WHO [1]. MAGI has been narrowly defined by the WHO concerning its relation to inflammation of distinct organs because data are lacking to confirm a generally negative influence of these urogenital infections on sperm quality and fertility. Urethritis and prostatitis are not always associated with male subfertility or infertility [58]. In many cases, basic ejaculate analysis does not reveal a link between accessory sex gland infection and impaired sperm characteristics. Furthermore, antibiotic treatment often only eradicates microorganisms; it has no positive effect on inflammatory alterations and/or cannot reverse functional deficits or anatomic and secretory dysfunctions [59,60].

## 13. Idiopathic male infertility

Many men presenting with infertility are found to have idiopathic OAT or idiopathic azoospermia. Idiopathic forms of male infertility are probably caused by genetic and environmental factors. It is predicted that >1000 genes are involved in spermatogenesis, but only a minority have been identified so far. Genetic factors may have direct cause-and-effect relationships or may predispose to infertility.

A combination of genetic predisposing and environmental factors (e.g., environmental pollution and reactive oxygen species) may result in testicular dysfunction and impaired sperm production.

## 14. Treatment

Infertility treatment should not start before 2 yr of unprotected intercourse, unless there are gross abnormalities found that exclude spontaneous pregnancy such as severe oligozoospermia or azoospermia, anovulation, tubal blockage, and female age >35 yr.

### 14.1. Counselling

According to the Charlson Comorbidity Index, infertile men have a significantly higher rate of comorbidity compared with fertile controls [61]. Certain lifestyle factors sometimes influence semen quality, for example, obesity, alcohol abuse, heavy smoking, use of anabolic steroids, extreme sports (marathon training or excessive strength sports), and increase in scrotal temperature through thermal underwear, sauna or hot tub use, or occupational exposure to heat sources. Many drugs can affect spermatogenesis [62].

### 14.2. Medical (hormonal) treatment

There is no evidence that hormonal therapies, such as human menopausal gonadotrophin (hMG)/human chorionic gonadotrophin (hCG), androgen, antioestrogens (clomiphene and tamoxifen), prolactin inhibitors (bromocriptine), and steroids improve pregnancy rates in partners of men with idiopathic OAT. However, hypogonadotrophic hypogonadism can be treated medically. The standard treatment is hCG, with the later addition of hMG or recombinant FSH, depending on initial testicular volume. In some cases of idiopathic hypogonadotrophic hypogonadism, spontaneous reversibility of reproductive function has been observed [63].

### 14.3. Empirical drug treatment

A wide variety of empirical drug approaches have been performed. However, the scientific evidence for such empirical approaches is low. Bromocriptine, hCG/hMG,  $\alpha$ -blockers, systemic corticosteroids, and magnesium supplementation are not effective for the treatment of idiopathic OAT. Androgens are strictly contraindicated. Recombinant FSH, folic acid with zinc, or antioestrogens may be beneficial in some patients. Cochrane analysis has shown that men taking oral antioxidants had a significant increase in live-birth rate (pooled odds ratio: 4.85; 95% CI, 1.92–12.24;  $p = 0.0008$ ,  $I^2 = 0\%$ ) when compared with men taking placebo. No studies have reported evidence of harmful side effects of antioxidant therapy. The evidence suggests that antioxidant supplementation in subfertile men may improve the outcomes of live birth and pregnancy rates for subfertile couples undergoing assisted reproduction techniques (ART) cycles. This conclusion is based on only 20 live births from a total of 214 couples. Further

head-to-head comparisons are necessary to identify the superiority of one antioxidant over another [64].

### 14.4. Surgical treatment

#### 14.4.1. Varicocele

An RCT comparing different surgical treatments of varicocele showed no clear benefit in favour of any technique in relation to improving sperm parameters. Also, pregnancy rates at 1 yr after surgery were comparable for open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy [65]. However, microscopic varicocelectomy is associated with significantly less recurrence and potentially fewer complications such as hydrocele, but it also requires more operating time and microsurgical training.

#### 14.4.2. Microsurgery/vasoepididymostomy

The indications for vasoepididymostomy include congenital and acquired obstructions at the level of the epididymis in the presence of normal spermatogenesis (testicular biopsy). Only urologists with experience in microsurgery should undertake this procedure [66]. Considering its limited effect on pregnancy rates (20–30%), ideally vasoepididymostomy/tubulovasostomy should be combined with microsurgical epididymal sperm aspiration (MESA) and cryopreservation of the harvested spermatozoa for future ICSI.

#### 14.4.3. Vasovasostomy

Vasovasostomy is best performed microscopically, which has been shown to be more effective in improving pregnancy rates [67]. The likelihood of initiating pregnancy is inversely proportional to the obstruction interval and becomes <50% after 8 yr; however, the obstruction interval appears to be less relevant when tubulovasostomy is performed for suspected secondary obstruction. Other prognostic factors are the development of sperm antibodies, semen quality, and partner's age. In approximately 20% of men who have undergone vasovasostomy, sperm quality deteriorates to the level of azoospermia or extreme oligospermia within 1 yr. Postoperative poor sperm quality frequently prevents spontaneous pregnancy, and ART is then indicated.

#### 14.4.4. Microsurgical epididymal sperm aspiration/testicular sperm extraction

MESA/TESE in combination with ICSI is indicated when reconstruction (vasovasostomy, epididymovasostomy) cannot be performed or is not successful. An alternative is percutaneous epididymal sperm aspiration (PESA) from the caput epididymis. If MESA or PESA does not produce spermatozoa or very low numbers of spermatozoa, a testicular biopsy can be performed with testicular sperm extraction (TESE) to be used for ICSI [68]. In patients with NOA due to testicular dysfunction, TESE is the only available option to retrieve spermatozoa for further use in ART. TESE should be performed on multiple locations in the testes. Microsurgical techniques may be used to identify testicular tubules with intact spermatogenesis [69]. In the presence of an AZFa and AZFb Y chromosome microdeletion, MESA/TESE is not advised.

#### 14.4.5. Transurethral resection of ejaculatory ducts or midline prostatic cysts

Distal obstructions of the genital tract are commonly caused by infections of the prostatic urethra and the accessory glands or by a cyst in the midline of the prostate. Treatment of the obstruction by transurethral incision of the cyst or the ejaculatory ducts may lead to an increase in semen quality and, occasionally, spontaneous pregnancy [70].

For further information, consult the *Extensive Guidelines on Male Infertility* (ISBN 90-806179-8-9), available to all members of the European Association of Urology on its Web site ([www.uroweb.org/guidelines/online-guidelines/](http://www.uroweb.org/guidelines/online-guidelines/)).

**Author contributions:** Andreas Jungwirth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Jungwirth.

**Acquisition of data:** Jungwirth, Giwercman, Tournaye, Diemer, Kopa, Dohle, Krausz.

**Analysis and interpretation of data:** Jungwirth, Giwercman, Tournaye, Diemer, Kopa, Dohle, Krausz.

**Drafting of the manuscript:** Jungwirth.

**Critical revision of the manuscript for important intellectual content:** Jungwirth, Giwercman, Tournaye, Diemer, Kopa, Dohle, Krausz.

**Statistical analysis:** Jungwirth.

**Obtaining funding:** None.

**Administrative, technical, or material support:** Jungwirth.

**Supervision:** Jungwirth.

**Other (specify):** None.

**Financial disclosures:** Andreas Jungwirth certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Andreas Jungwirth receives company speaker honoraria from Pfizer Austria, Eli Lilly, Bayer Schering Healthcare, and Janssen Cilag, and he participates in trials for Janssen Cilag and Eli Lilly. Aleksander Giwercman is a company consultant for Bayer-Schering. He participates in trials for ProStrakan and Bayer-Schering, and receives research grants for Merck-Serono and Ferring. Herman Tournaye receives research grants from Ferring. Thorsten Diemer has equity interests in Lilly Deutschland via a family member and a family member who is an employee there. He receives company speaker honoraria from Bayer Vital, Bayer Healthcare, and American Medical Systems. He receives research grants from Takeda Pharma. Zsolt Kopa is a company consultant and receives company speaker honoraria from Bayer-Schering, Pfizer, and Lilly. Gert Dohle has nothing to disclose. Csilla Krausz had a one-year grant from Biocell Milan for research in 2007.

**Funding/Support and role of the sponsor:** None.

## References

- [1] World Health Organisation. WHO manual for the standardised investigation and diagnosis of the infertile couple. Cambridge, UK: Cambridge University Press; 2000.
- [2] Te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update* 2002;8:141–54.
- [3] Nieschlag E, Behre HM, editors. *Andrology: male reproductive health and dysfunction*. ed. 2. Berlin, Germany: Springer-Verlag; 2001. p. 83–7.
- [4] Pierik FH, Van Ginneken AM, Dohle GR, et al. The advantages of standardized evaluation of male infertility. *Int J Androl* 2000;23:340–6.
- [5] Rowe T. Fertility and a woman's age. *J Reprod Med* 2006;51:157–63.
- [6] World Health Organisation. WHO laboratory manual for the examination and processing of human semen. ed. 5. Geneva, Switzerland: WHO; 2010.
- [7] Bungum M, Bungum L, Lynch KF, et al. Spermatozoa DNA damage measured by sperm chromatin structure assay (SCSA) and birth characteristics in children conceived by IVF and ICSI. *Asian J Androl* 2011;13:68–75.
- [8] Weber RF, Dohle GR, Romijn JC. Clinical laboratory evaluation of male subfertility. *Adv Clin Chem* 2005;40:317–64.
- [9] La Vignera S, Vicari E, Condorelli RA, et al. Male accessory gland infection and sperm parameters. *Int J Androl* 2011;34:330–47.
- [10] Elzinga-Tinke JE, Sirre ME, Looijenga LH, et al. The predictive value of testicular ultrasound abnormalities for carcinoma in situ of the testis in men at risk for testicular cancer. *Int J Androl* 2010;33:597–603.
- [11] Colpi GM, Negri L, Nappi RE, et al. Is transrectal ultrasonography a reliable diagnostic approach in ejaculatory duct sub-obstruction? *Hum Reprod* 1997;12:2186–91.
- [12] Schlegel PN, Palermo GD, Goldstein M, et al. Testicular sperm extraction with intracytoplasmic sperm injection for nonobstructive azoospermia. *Urology* 1997;49:435–40.
- [13] Holm M, Hoei-Hansen CE, Rajpert-De Meyts E, et al. Increased risk of carcinoma in situ in patients with testicular germ cell cancer with ultrasonic microlithiasis in the contralateral testicle. *J Urol* 2003;170:1163–7.
- [14] Hendry WF, Parslow JM, Stedronska J. Exploratory scrototomy in 168 azoospermic males. *Br J Urol* 1983;55:785–91.
- [15] Schoysman R. Vaso-epididymostomy—a survey of techniques and results with considerations of delay of appearance of spermatozoa after surgery. *Acta Eur Fertil* 1990;21:239–45.
- [16] Jequier AM. Obstructive azoospermia: a study of 102 patients. *Clin Reprod Fertil* 1985;3:21–36.
- [17] Dohle GR, Diemer T, Kopa Z, et al., European Association of Urology Working Group on Male Infertility. European Association of Urology guidelines on vasectomy. *Eur Urol* 2012;61:159–63.
- [18] Oates RD, Amos JA. The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis. *J Androl* 1994;15:1–8.
- [19] Handelsman DJ, Conway AJ, Boylan LM, et al. Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. *N Engl J Med* 1984;310:3–9.
- [20] Meacham RB, Hellerstein DK, Lipshultz LI. Evaluation and treatment of ejaculatory duct obstruction in the infertile male. *Fertil Steril* 1993;59:393–7.
- [21] Pryor JP, Hendry WF. Ejaculatory duct obstruction in subfertile males: analysis of 87 patients. *Fertil Steril* 1991;56:725–30.
- [22] Johnson MD. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. *Fertil Steril* 1998;70:397–411.
- [23] van Assche EV, Bonduelle M, Tournaye H, et al. Cytogenetics of infertile men. *Hum Reprod* 1996;11(Suppl 4):1–24.
- [24] Vincent MC, Daudin M, De MP, et al. Cytogenetic investigations of infertile men with low sperm counts: a 25-year experience. *J Androl* 2002;23:18–22.
- [25] Lanfranco F, Kamischke A, Zitzmann M, et al. Klinefelter's syndrome. *Lancet* 2004;364:273–83.
- [26] Ramasamy R, Ricci JA, Palermo GD. Successful fertility treatment for Klinefelter's syndrome. *J Urol* 2009;182:1108–13.
- [27] Staessen C, Tournaye H, Van Assche E, et al. PGD in 47,XXY Klinefelter's syndrome patients. *Hum Reprod Update* 2003;9:319–30.

- [28] Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* 2003;423:825–37.
- [29] Vogt PH, Edelmann A, Kirsch S, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Hum Mol Genet* 1996;5:933–43.
- [30] Kausz C, Degl'Innocenti S. Y chromosome and male infertility: update, 2006. *Front Biosci* 2006;11:3049–61.
- [31] Simoni M, Bakker E, Krausz C. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions. State of the art 2004. *Int J Androl* 2004;27:240–9.
- [32] Krausz C, Chianese G, Giachini C, et al. The Y chromosome-linked copy number variations and male fertility. *J Endocrinol Invest* 2011;34:376–82.
- [33] De Braekeleer M, Ferec C. Mutations in the cystic fibrosis gene in men with congenital bilateral absence of the vas deferens. *Mol Hum Reprod* 1996;2:669–77.
- [34] [No authors listed]. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organisation. *Fertil Steril* 1992;57:1289–93.
- [35] Argawal A, Deepinder F, Cocuzza M, et al. Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach. *Urology* 2007;70:532–8.
- [36] Zini A, Dohle G. Are varicoceles associated with increased deoxyribonucleic acid fragmentation? *Fertil Steril* 2011;96:1283–7.
- [37] Evers JH, Collins J, Clarke J. Surgery or embolisation for varicoceles in subfertile men. *Cochrane Database Syst Rev* 2009:CD000479.
- [38] Ficarra V, Cerruto MA, Liguori G, et al. Treatment of varicocele in subfertile men: the Cochrane review—a contrary opinion. *Eur Urol* 2006;49:258–63.
- [39] Grasso M, Lania M, Castelli M, et al. Lowgrade left varicocele in patients over 30 years old: the effect of spermatic vein ligation on fertility. *BJU Int* 2000;85:305–7.
- [40] Yamamoto M, Hibi H, Hirata Y, et al. Effect of varicocelectomy on sperm parameters and pregnancy rates in patients with subclinical varicocele: a randomized prospective controlled study. *J Urol* 1996;155:1636–8.
- [41] Unal D, Yeni E, Verit A, et al. Clomiphene citrate versus varicocelectomy in treatment of subclinical varicocele: a prospective randomized study. *Int J Urol* 2001;8:227–30.
- [42] Nilsson S, Edvinsson A, Nilsson B. Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: fact or fiction? *Br J Urol* 1979;51:591–6.
- [43] Breznik R, Vlasisavljevic V, Borko E. Treatment of varicocele and male fertility. *Arch Androl* 1993;30:157–60.
- [44] Giagulli VA, Carbone MD. Varicocele correction for infertility: which patients to treat? *Int J Androl* 2011;34:236–41.
- [45] Baazeem A, Belzile E, Ciampi A, et al. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol* 2011;60:796–808.
- [46] Zargooshi J. Sperm count and sperm motility in incidental high-grade varicocele. *Fertil Steril* 2007;88:1470–3.
- [47] Layman LC. Hypogonadotropic hypogonadism. *Endocrinol Metab Clin North Am* 2007;36:283–96.
- [48] Trarbach EB, Silveira LG, Latronico AC. Genetic insights into human isolated gonadotropin deficiency. *Pituitary* 2007;10:381–91.
- [49] Huhtaniemi I, Alevizaki M. Mutations along the hypothalamic-pituitary-gonadal axis affecting male reproduction. *Reprod Biomed Online* 2007;15:622–32.
- [50] Skakkebaek NS, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome; an increasingly common developmental disorder with environmental aspects. *Human Reprod* 2001;16:972–8.
- [51] Hadziselimovic F. Cryptorchidism, its impact on male fertility. *Eur Urol* 2002;41:121–3.
- [52] Miller KD, Coughlin MT, Lee PA. Fertility after unilateral cryptorchidism. Paternity, time to conception, pretreatment testicular location and size, hormone and sperm parameters. *Horm Res* 2001;55:249–53.
- [53] Lee PA, Coughlin MT. Fertility after bilateral cryptorchidism. Evaluation by paternity, hormone, and semen data. *Horm Res* 2001;55:28–32.
- [54] Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? *Lancet Oncol* 2005;6:209–18.
- [55] Dieckmann KP, Skakkebaek NE. Carcinoma in situ of the testis: review of biological and clinical features. *Int J Cancer* 1999;83:815–22.
- [56] van Casteren NJ, Dohle GR, Looijenga LH. Testicular microlithiasis is worrisome in a selected patient population. *Curr Opin Urol* 2008;18:436.
- [57] Purvis K, Christiansen E. Infection in the male reproductive tract. Impact, diagnosis and treatment in relation to male infertility. *Int J Androl* 1993;16:1–13.
- [58] Schaeffer AJ, Weidner W, Barbalias GA, et al. Summary consensus statement: diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome. *Eur Urol Suppl* 2003;2(2):1–4.
- [59] Weidner W, Wagenlehner FM, Marconi M, et al. Acute bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: andrological implications. *Andrologia* 2008;40:105–12.
- [60] Wagenlehner FM, Diemer T, Naber KG, et al. Chronic bacterial prostatitis (NIH type II): diagnosis, therapy and influence on the fertility status. *Andrologia* 2008;40:100–4.
- [61] Salonia A, Matloob R, Gallina A, et al. Are infertile men less healthy than fertile men? Results of a prospective case-control survey. *Eur Urol* 2009;56:1025–32.
- [62] Practise committee of American Society for Reproductive Medicine in collaboration with Society for Reproductive Endocrinology and Infertility. Optimizing natural fertility. *Fert Steril* 2008;90(Suppl): S1–6.
- [63] Pitteloud N, Acierno Jr JS, Meysing AU, et al. Reversible Kallmann syndrome, delayed puberty, and isolated anosmia occurring in a single family with a mutation in the fibroblast growth factor receptor 1 gene. *J Clin Endocrinol Metab* 2005;90:1317–22.
- [64] Showell MG, Brown J, Yazdani A, et al. Antioxidants for male subfertility. *Cochrane Database Syst Rev* 2011:CD007411.
- [65] Al-Kandari AM, Shabaan H, Ibrahim HM, et al. Comparison of outcomes of different varicocelectomy techniques: open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy: a randomized clinical trial. *Urology* 2007;69:417–20.
- [66] Marmar JL. Modified vasoepididymostomy with simultaneous double needle placement, tubulotomy and tubular invagination. *J Urol* 2000;163:483–6.
- [67] Silber SJ, Grotjan HE. Microscopic vasectomy reversal 30 years later: a summary of 4010 cases by the same surgeon. *J Androl* 2004;25:845–59.
- [68] Tournaye H. Surgical sperm recovery for intracytoplasmic sperm injection: which method is to be preferred? *Hum Reprod* 1999;14(Suppl 1):71–81.
- [69] Colpi GM, Colpi EM, Piediferro G, et al. Microsurgical TESE versus conventional TESE for ICSI in non-obstructive azoospermia: a randomized controlled study. *Reprod Biomed Online* 2009;18:315–9.
- [70] Schroeder-Printzen I, Ludwig M, Köhn F, et al. Surgical therapy in infertile men with ejaculatory duct obstruction: technique and outcome of a standardized surgical approach. *Hum Reprod* 2000;15:1364–8.