Sexual dysfunction and male infertility.

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Sexual dysfunction and male infertility

*Francesco Lotti and Mario Maggi**

Abstract | Infertility affects up to 12% of all men, and sexual dysfunction occurs frequently in men of reproductive age, causing infertility in some instances. In infertile men, hypoactive sexual desire and lack of sexual satisfaction are the most prevalent types of sexual dysfunction, ranging from 8.9% to 68.7%. Erectile dysfunction and/or premature ejaculation, evaluated with validated tools, have a prevalence of one in six infertile men, and orgasmic dysfunction has a prevalence of one in ten infertile men. In addition, infertile men can experience a heavy psychological burden. Infertility and its associated psychological concerns can underlie sexual dysfunction. Furthermore, general health perturbations can lead to male infertility and/or sexual dysfunction. Erectile dysfunction and male infertility are considered proxies for general health, the former underlying cardiovascular disorders and the latter cancerous and noncancerous conditions. The concept that erectile dysfunction in infertile men might be an early marker of poor general health is emerging. Finally, medications used for general health problems can cause sperm abnormalities and sexual dysfunction. The treatment of some causes of male infertility might improve semen quality and reverse infertility-related sexual dysfunction. In infertile men, an investigation of sexual, general, and psychological health status is advisable to improve reproductive problems and general health.

Couple infertility and sexual dysfunction are two frustrating conditions with a high prevalence in the general population. Infertility has been recognized as a public health issue by the WHO[1]; however, no reliable figures exist regarding its global prevalence[2]. In 2006, the prevalence of couple infertility was estimated to be 72.4 million globally according to a study evaluating 25 population surveys that sampled ~170,000 women[1]. However, another study used a larger data set derived from 277 demographic and reproductive health surveys and reported infertility in 45.5 million couples in 2010 (REF. 3). Overall, the median prevalence of couple infertility has been estimated to be 9%, with rates of 3.5–16.7% in developed countries and 6.9–9.3% in less developed countries[1]. A large epidemiological survey by the WHO[4] found that a pure or combined male factor contributes to infertility in about half of couples. In addition, a 2013 study evaluating 22,682 interviews of men and women aged 15–44 years reported that in the USA, up to 12% of men have fertility problems[5].

Sexual dysfunction in men is often present in the general population, with 20–30% of adult men globally reporting at least one sexual disorder[6,7] and prevalence increasing with increased age[7]. To date, validated tools for the assessment of male sexual dysfunction are available only for the study of erectile dysfunction and premature ejaculation. The estimated prevalence of erectile dysfunction and premature ejaculation in men of reproductive age ranges from 12% to 19%[7–13] and from 8% to 31%[7,12,13], respectively. This observation is noteworthy, considering the high frequencies in relatively young men. Erectile dysfunction and premature ejaculation are common types of male sexual dysfunction, but, since 2012, their prevalence in infertile men has only been assessed by a few investigators, using heterogeneous tools, none of which had been validated for the study of premature ejaculation and only a few for erectile dysfunction (TABLE 1). Only a few studies[14–16] have investigated erectile dysfunction and premature ejaculation in infertile men using validated instruments, reporting a higher frequency of erectile dysfunction[14–16] and a similar[14,15] or higher[16] prevalence of premature ejaculation in the men who were part of an infertile couple than is observed in the general population of men of a similar age.

A possible link between male infertility and sexual dysfunction is represented by the psychopathological disturbances associated with both conditions, such as anxiety and depression. Several studies have investigated the psychological burden of infertile men[17–19], but only a few have focused on mood disturbances in infertile patients with sexual dysfunction[14–16,20,21].

Decreased general health status is associated with impaired male sexual[22] and reproductive[23] health. The

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Key points

- Infertility affects up to 12% of all men, and sexual dysfunction occurs frequently in men of reproductive age, causing infertility in some instances
- Infertile men can experience a heavy psychological burden. Infertility and its associated psychological concerns can underlie sexual dysfunction
- General health perturbations can lead to male infertility and/or sexual dysfunction. Erectile dysfunction and male infertility are considered proxies for general health
- Medications used for general health problems can cause sperm abnormalities and sexual dysfunction. The treatment of some causes of male infertility might improve semen quality and reverse infertility-related sexual dysfunction
- In infertile men, an investigation of sexual, general, and psychological health status is advisable to improve reproductive problems and general health.

concept that male infertility might be an early marker of poor general health is emerging[15,24–27].

In this Review, we discuss the correlations between sexual dysfunction and male infertility, focusing on the associations between reproductive, sexual, psychological, and general health.

Sexual dysfunction causes infertility

Prevalence in male infertility

Sexual dysfunction is a rare cause of male infertility[14,28,29]. According to the WHO[4], which performed the first large study on the aetiology of male infertility ($n = 7,273$), sexual dysfunction accounts for 2.3% of instances of unsuccessful fatherhood. In 2000, a single-centre study[30] reported sexual dysfunction as a cause of male infertility in 4.6% of 1,549 men. Subsequently, further studies reported different frequencies, ranging from 0.4% in a series of 1,391 subfertile couples[31] to 5% in a small cohort ($n = 98$) of infertile couples[32]. The European Association of Urology (EAU)[33] reports a prevalence of 2.4%, derived from a cohort of 12,945 patients[34]. Finally, a 2017 study including 1,737 patients with severe male factor infertility reported severe sexual dysfunction as a primary cause of infertility in 4.4% of men[35]. In particular, anorgasmia, anejaculation, total retrograde ejaculation, and partial retrograde ejaculation accounted for 0.5%, 1.2%, 0.5%, and 2.2% of the causes of infertility, respectively[35]. Severe sexual dysfunction was found to be the main causative factor (71.1%) in patients with dry ejaculate[35]. Thus, sexual dysfunction could be the cause of male infertility in 0.4–4.6% of infertile men.

Types of dysfunction causing infertility

The aetiology of male infertility is related to pretesticular, testicular or post-testicular factors by some investigators[28,36], considering the topographical localization of the cause. According to this classification[28,36], sexual dysfunction is categorized as a pretesticular cause of male infertility[28,36]. Other authors[34], who used a more detailed classification and relied on the International Classification of Diseases (ICD)-10 (REF. 37) codes of disorders leading to male infertility, classify sexual dysfunction in a category named disturbed semen deposition. Types of sexual dysfunction resulting in male infertility include erectile dysfunction and ejaculatory disorders, such as anejaculation, retrograde ejaculation, and severe premature ejaculation, depending on organic, iatrogenic, relational, and/or psychogenic causes (BOX 1). Of note, male fertility can be impaired by sexual dysfunction per se, such as in the case of psychogenic erectile dysfunction, or, more often, infertility can be caused by the negative effect exerted on semen parameters by a systemic disease or by the medication used to treat such diseases, which can also lead to sexual dysfunction.

Erectile dysfunction. Erectile dysfunction leads to impaired fertility through natural conception when a severe problem is present, such as absent erection or insufficient erection for penetration. Erectile dysfunction can be caused by organic (such as cardiovascular, metabolic, neurogenic, and endocrine factors; BOX 1), relational (such as conflicts within the family and/or within the couple), and/or intrapsychic (such as anxiety, depression) perturbations[38]. In addition, among infertile men, erectile dysfunction is an independent risk factor for a reduced frequency of sexual intercourse with an obvious negative effect on fertility[39]. Treatment of erectile dysfunction includes lifestyle modifications, oral and parenteral drugs, injectable vasodilator agents, vacuum erection devices, surgery, or psychosexual therapy, either individually or involving both partners of the couple[38,40].

Ejaculatory disorders. Ejaculatory disorders affecting male fertility are mainly those resulting in aspermia (dry ejaculate), which can occur either because of an inability to transport semen (anejaculation) or because of an inability to ejaculate in an antegrade direction (retrograde ejaculation)[41].

Anejaculation is the inability to ejaculate through any form of stimulation[42,43]. This condition is relatively rare, occurring in 0.14% of the general population[44], but is an important determinant of male infertility[42]. Anejaculation frequently occurs in men with conditions affecting the nervous system, including organic and iatrogenic causes[42,43,45–47] (BOX 1), but it can also be related to medications (such as psychotropic drugs)[42,45] or psychogenic[48] causes (BOX 1). The most common causes of anejaculation are retroperitoneal lymph node dissection (RPLND) and spinal cord injury (SCI), which together account for almost 90% of instances[45]. RPLND is mainly performed in men with testis malignancy[42]. As a testicular tumour is the most frequent malignancy in males of reproductive age[49], RPLND can widely affect the fertility of young men. Ejaculatory function is lost in 1–19% of men after a nerve-sparing procedure[45,47,50,51], but this figure rises to >20% when post-chemotherapy retroperitoneal fibrosis makes it difficult to spare nerves[45,46]. Regarding SCI, only 9% of men can achieve ejaculation via masturbation or sexual intercourse[46,52], and ~95% of SCI patients are unable to procreate without medical intervention[42,52].

Retrograde ejaculation occurs when the contraction of the pelvic muscles associated with the orgasmic sensation is not followed by semen expulsion[43]. This phenomenon is caused by incomplete closure of the internal sphincter of the bladder, leading to retrograde (backwards) ejaculation into the bladder[43]. Diagnosis of

Table 1 | **Studies evaluating sexual dysfunctions in infertile men**

Refs	Number of infertile patients	Number of fertile men (control group)	Sexual dysfunctions in infertile men				
			Erectile dysfunction	Premature ejaculation	Hypoactive sexual desire disorder	Satisfaction impairment	Orgasmic dysfunction
58	16	NA	69% NVQ	NA	NA	NA	NA
59	16	NA	69% NVQ	NA	NA	NA	NA
73	514	NA	17.1%, NVQ	13.5%, NVQ	68.7%, NVQ	NA	NA
100	43	NA	NA	NA	NA	No changes in sexual satisfaction after infertility diagnosis	NA
57	40	NA	NA	75%, NVQ	NA	NA	NA
96	157	NA	NA	NA	NA	• High rates of low sexual satisfaction • NVQ	NA
101	68	NA	NA	NA	NA	• High rates of low sexual satisfaction • NVQ	NA
74	175	NA	15%, NVQ	66%, NVQ	11%, NVQ	NA	8%, NVQ
60	405	NA	11%, IIEF-5	NA	NA	NA	NA
98	18	12	NA	NA	NA	• Lower sexual satisfaction in infertile men than in controls • IIEF-15	NA
62	302	NA	28%, IIEF-5	NA	NA	NA	NA
88	200	NA	NA	NA	45.4%, NVQ	• Low sexual satisfaction in 52.5% of patients after infertility diagnosis • NVQ	NA
65	100	NA	61.6%, IIEF-15-EFD	NA	NA	NA	NA
21	73	NA	NA	50%, NVQ	NA	NA	NA
97	357	NA	NA	NA	NA	• Low sexual satisfaction in subjects with male factor infertility • NVQ	NA
95	188	190	NA	NA	NA	• Male factor infertility scores low sexual satisfaction; however, no sexual satisfaction difference in infertile versus fertile men • Validated ISS	NA
75	300	NA	NA	43%, NVQ	NA	NA	NA
91	156	NA	23.7%, IIEF-5	NA	8.9%, IIEF-5	NA	NA
14[a]	244	NA	17.8%, IIEF-15-EFD	15.6%, PEDT	NA	NA	NA
56[a]	60	52	• 33.2%, IIEF-15 • Men with a recent (<2 months) diagnosis of infertility show lower EFD score than fertile men (26.6%: men with a recent diagnosis of infertility; 6.7%: men in infertile couples already undergoing IUI)	NA	Infertile men show lower sexual desire than fertile men; IIEF-15	Infertile men show lower sexual and overall satisfaction than fertile men IIEF-15	Men with a recent (<3 months) diagnosis of infertility show a lower orgasmic function score than fertile men; IIEF-15

Table 1 (cont.) | **Studies evaluating sexual dysfunctions in infertile men**

Refs	Number of infertile patients	Number of fertile men (control group)	Sexual dysfunctions in infertile men				
			Erectile dysfunction	Premature ejaculation	Hypoactive sexual desire disorder	Satisfaction impairment	Orgasmic dysfunction
16[a]	1,498	942	18.05%, IIEF-15-EFD	19.01%, PEDT	NA	NA	NA
63[a]	1,750	NA	30.5%, IIEF-5	NA	NA	NA	NA
99[a]	153	NA	NA	NA	NA	• Reduced sexual satisfaction • SEAR	NA
20[a]	236	NA	50.8%, IIEF-5	NA	NA	NA	NA
15[a]	488	74	18.3%, IIEF-15-EFD	12.9%, PEDT	Men with azoospermia men show a lower sexual desire score than fertile men; IIEF-15	No difference in sexual satisfaction comparing males of infertile and fertile couples IIEF-15	Men with azoospermia men have lower orgasmic function score than fertile men; IIEF-15

EFD, erectile function domain; IIEF, International Index of Erectile Function; ISS, Index of Sexual Satisfaction; IUI, intrauterine insemination; NA, not applicable; NVQ, not validated questionnaire; PEDT, Premature Ejaculation Diagnostic Tool; SEAR, Self-Esteem and Relationship Questionnaire. [a]Studies published since 2012.

retrograde ejaculation is based on the absence of spermatozoa in the seminal fluid when they are present in urine after masturbation[28]. Retrograde ejaculation is the only ejaculatory disorder that is exclusively organic in origin[53]. Causes of retrograde ejaculation are classified as pharmacological, neurogenic and anatomic[53], or organic and iatrogenic (BOX 1) and include any factor disrupting the ejaculatory reflex and inhibiting bladder neck contraction[53]. Apart from iatrogenic causes, diabetes mellitus is the main aetiological factor causing retrograde ejaculation[43]. The frequency of this disorder in patients with diabetes (both types 1 and 2) ranges from 6% to 40%[43,46]. The estimated prevalence of retrograde ejaculation in patients attending fertility clinics[43,53] ranges from 0.3% to 2%.

The severity of the ejaculatory dysfunction depends upon the severity of sympathetic autonomic neuropathy[46]. Anejaculation or retrograde ejaculation can also occur in other conditions affecting the peripheral nervous system, such as multiple sclerosis. In multiple sclerosis, ejaculatory dysfunction is estimated to be present in approximately 50% of patients[42,45,46]. One study[54] reported that in 128 non-spinal-cord injured consecutive patients with organic anejaculation, 17 had multiple sclerosis. In a prospective randomized placebo-controlled double-blind study, the authors[54] found that out of eight subjects with multiple sclerosis treated with midodrine, four achieved antegrade ejaculation and two achieved retrograde ejaculation (one with a complete form and one with a partial form).

The treatment of aspermia varies depending on the underlying aetiology and includes medical therapy with sympathomimetics, urinary sperm retrieval, bladder neck reconstruction, prostatic massage, penile vibratory stimulation, electroejaculation, and surgical sperm retrieval from the testis or epididymis[41]. Intracytoplasmatic sperm injection (ICSI) is the main reliable option for achieving pregnancy for men with aspermia[28]. In subjects with anejaculation, testicular sperm extraction (TESE) is frequently used to retrieve sperms from the testes to be used for ICSI[41]. In retrograde ejaculation, spermatozoa retrieved from urine can also be used for ICSI. In order to optimize spermatozoa motility, the WHO manual (2010)[55] recommends alkalinizing the urine by ingesting sodium bicarbonate and concentrating the retrograde specimen using the density-gradient preparation method. This method uses centrifugation of seminal plasma over density gradients consisting of colloidal silica coated with silane, which separates cells by their density[55]. Motile sperm actively swim through the gradient material to form a soft pellet at the bottom of the tube. Sperm preparation using density-gradient centrifugation results in a fraction of highly motile sperms free from debris and other cells[55].

Premature ejaculation. Severe premature ejaculation, including ejaculation during foreplay, before penetration (anteportal ejaculation), or as soon as the penis touches the vagina, is a barrier to natural conception, because the sperm fails to enter the vagina[6,48]. In these circumstances, treatment including drugs for acquired or lifelong premature ejaculation and/or psychosexual therapy, or assisted reproductive technology (ART) when premature ejaculation is resistant to therapy, can help in obtaining pregnancy.

Male infertility as a cause of sexual dysfunction

The prevalence of sexual dysfunction in infertile men ranges between 6.7%[56] and 75%[57] (TABLE 1). Notably, infertility can exert a detrimental effect on sexual, psychological, and marital life of both partners in the couple[17,18], and the presence of a simultaneous female disorder can negatively affect the couple's sexual response. In fact, women in infertile couples might experience sexual dysfunction, such as hypoactive sexual desire, arousal dysfunction, anorgasmia, dyspareunia, and vaginismus, as well as anxiety, depression, and difficulties in marital relationships[17,18], which can in turn

Box 1 | **Sexual dysfunctions that might lead to male infertility**[22,38,42,43,48,53,123]

Erectile dysfunction

- *Organic causes*
  - Cardiovascular
  - Metabolic
  - Neurogenic
  - Endocrine
- *Iatrogenic causes*
  - Pelvic surgery
  - Radiotherapy
  - Drugs
- *Relational causes*
- *Psychogenic causes*

Anejaculation

- *Organic causes*
  - Spinal cord injury
  - Diabetic neuropathy
  - Multiple sclerosis
  - Transverse myelitis
  - Vascular spine injuries
  - Congenital spinal anomalies (such as spina bifida)
  - Hormonal disorders (hyperprolactinaemia, hypogonadism, and hypothyroidism)
- *Iatrogenic causes*
  - Retroperitoneal lymph node dissection
  - Prostatectomy
  - Rectal surgery
  - Pelvic radiation
  - Drugs (psychotropic drugs and α-blockers)
- *Relational causes*
- *Psychogenic causes* (such as fear, anxiety, hostility, relationship difficulties, orthodoxy of religious belief, autosexual orientation, and disparity between sex reality and the use of sexual fantasy)

Retrograde ejaculation

- *Organic causes*
  - Spinal cord injury
  - Diabetic neuropathy
  - Multiple sclerosis
  - Myelodysplasia
  - Cerebrovascular accidents
  - Congenital (posterior urethral valves, utricular cysts, and extrophy)
- *Iatrogenic causes*
  - Lumbar sympathectomy
  - Retroperitoneal lymph node dissection
  - Aortoiliac vascular surgery
  - Abdominoperineal resection
  - Transurethral bladder neck incision and transurethral resection of prostate
  - Drugs (psychotropic drugs)

Premature ejaculation

- *Organic causes*
  - Male genital tract inflammation
  - Hyperthyroidism (varicocele)
- *Iatrogenic causes*
  - Psychotropic drugs
- *Relational causes*
- *Psychogenic causes*

trigger or worsen male sexual dysfunction. Thus, infertility-related male sexual dysfunction can be affected by confounders, such as the presence of female sexual and psychological disorders.

Erectile dysfunction

The prevalence of erectile dysfunction in infertile men has been assessed by a few investigators and is relatively novel research (TABLE 1). The first reports on this issue were from Berger in 1980 (REFS 58,59), who observed that 11 men in a small cohort of 16 couples experienced impotency after discovering they were infertile, using a nonvalidated tool. In 2003, Saleh et al.[60] reported that 11% of men undergoing infertility evaluation after detection of abnormal results in their first semen analysis experienced erectile problems when assessed by the validated instrument International Index of Erectile Function (IIEF)-5 in a larger series ($n = 405$)[61]. Using the same tool[61], O'Brien et al.[62] and Satkunasivam et al.[63] found frequencies of erectile dysfunction in infertile men of 28% ($n = 302$) and 30.5% ($n = 1,750$), respectively. In a smaller cohort ($n = 30$), Marci et al.[56] found that prevalence of erectile dysfunction was 26.6% in 30 men who had been recently (within two months) diagnosed with primary infertility and 6.7% in 30 infertile men who were part of a couple who were undergoing intrauterine insemination used the IIEF-15-erectile function domain (IIEF-15-EFD)[64]. Subsequent studies using the IIEF-15-EFD reported that prevalence of erectile dysfunction was ~18% in cohorts of 244 (REF. 14) and 448 (REF. 15) men in infertile couples. A study performed in a Chinese population ($n = 1,498$) also reported an 18% prevalence of erectile dysfunction in infertile men[16]. Hence, a prevalence of 11–30.5% has been reported in studies investigating a relatively large cohort of men with couple infertility[15,16,60,62,63]. Notably, two other studies have been published on this topic, finding a higher prevalence of erectile dysfunction in infertile men than in those discussed above. Khademi et al.[65] found the frequency of erectile dysfunction to be 61.6% in 100 infertile men, using the IIEF-15-EFD, and Song et al.[20] reported a prevalence of 50.8% in 236 men in infertile couples using the IIEF-5. Khademi et al.[65] speculated that the different frequencies reported compared with other studies were caused by increased rates of mild-to-moderate erectile dysfunction in their population. Notably, a high percentage of infertile men who had mild (32.3%) or mild-to-moderate (22.2%) erectile dysfunction was reported by Khademi and colleagues[65], whereas 42% of men had a mild form of erectile dysfunction in the study by Song and co-workers[20]. The reason why such a high prevalence of erectile dysfunction was found in these studies[20,65] is difficult to determine. Possibly, the patients evaluated could have been seeking medical care not only for infertility but also for sexual dysfunction, owing to the high prevalence of erectile dysfunction in the populations studied[20,56]. Hence, considering the studies investigating erectile dysfunction in infertile men, its prevalence ranges from 6.7%[56] to 61.6%[65].

Erectile dysfunction increases as a function of severity of semen quality impairment, being higher in men with azoospermia than in men in infertile couples with at least one abnormality in conventional sperm parameters or with normozoospermia[15], and than in fertile men[15].

All the available studies comparing the erectile function of men who are part of an infertile couple and those who are members of a fertile couple found a significantly increased prevalence of erectile dysfunction in infertile men ($P = 0.006$ (REF. 15); $P < 0.001$ (REF. 16); $P = 0.007$ (REF. 62); $P < 0.0005$ (REF. 56)). In addition, the frequency of erectile dysfunction in infertile men has been reported as higher than that of age-matched and geographically matched men in the general population[14,16,66]. However, frequency of erectile dysfunction increases with age and its related comorbidities, including hypogonadism; thus, the demonstration of an independent association between erectile dysfunction and infertility is difficult. One study[15] reported a significant association between erectile dysfunction and semen quality impairment after adjusting for age, comorbidities, and psychological and prostatitis-like symptoms ($P < 0.0001$). No differences in serum testosterone levels were observed[15]. In 2017, Sahin et al.[67] reported an association between erectile dysfunction and depressive symptoms independent of age, BMI, and duration of marriage in a small but select cohort of men without comorbidities with primary ($n = 39$) or secondary ($n = 31$) infertility. Similar findings were observed in both subgroups of participants, but men with secondary infertility were older, had older partners, longer marriage duration, higher erectile dysfunction rates, and higher depression rates than men with primary erectile dysfunction[67]. These figures are expected in men with secondary infertility, but the main implication of this study[67] is that erectile dysfunction is independently associated with depressive symptoms regardless of the type of infertility (primary or secondary) in infertile men.

The simultaneous presence of sexual dysfunction in the female partner of an infertile couple could contribute to the deterioration of erectile function[17,18]. Women with secondary infertility had lower scores on the Female Sexual Function Index in the orgasm[68], satisfaction[68], arousal[69], and desire[70] subdomains than women with primary infertility. In addition, it could be speculated that the presence of children could further impair a couple's sexuality in secondary infertility. No specific study on this topic has been performed on men with secondary infertility; however, studies investigating the association of fatherhood and sexual dysfunction have been performed in cohorts of men primarily complaining of sexual dysfunction. One study[71] reported that increasing numbers of children are associated with an increasing severity of lack of sexual privacy, and that the latter is associated with mild erectile dysfunction, particularly with regards to intrapsychic and relational, but not organic, domains, measured using the scales of the Structured Interview on Erectile Dysfunction (SIEDY). Another study reported that an increasing number of children is associated with a decrease in testosterone levels and with a worse metabolic and cardiovascular profile, as well as worse penile blood flow in men with sexual dysfunction[72]. Thus, the lack of privacy experienced by couples with secondary infertility could be a factor that negatively affects sexual function. Hence, similar studies in an infertility setting are advisable.

Ejaculatory disorders

The prevalence of ejaculatory disorders in infertile men has been investigated with validated instruments by a few researchers[15–17]. Since 2012, a limited number of studies have assessed premature ejaculation in infertile men, using unvalidated tools (TABLE 1). One study showed a prevalence of premature ejaculation in infertile men of 13.5%[73], but the majority of the authors reported higher rates, such as 75%[57], 66%[74], 50%[21], and 43%[75], in relatively small cohorts (TABLE 1). These frequencies[21,57,74,75] are similar to those reported by previous studies (75%[44] and 69%[76]) but higher than those reported by other authors (31%[8], 15%[12], 31%[13], and 36%[77]) in the general population. Studies involving more participants than the studies published since 2012 that used a validated instrument for assessing premature ejaculation (such as the Premature Ejaculation Diagnostic Tool[78]) reported a frequency of premature ejaculation in men in infertile couples of 15.6%[14], 19%[16], and 12.9%[15]. The prevalence of premature ejaculation reported in studies in the Italian population of infertile men[14,15] was similar to that found in the general Italian population[11] (11.6%), whereas the prevalence observed by Gao et al.[16] in a Chinese population of infertile men was higher than that of a comparative study in the general Chinese population[79] (11%).

Hassanzadeh et al.[75] found that in 300 infertile Iranian men, 129 had premature ejaculation, of whom 74% had the lifelong form, and 26% had acquired premature ejaculation. These figures are similar to those reported by Serefoglu et al.[80] in 261 Turkish men admitted to an urology outpatient clinic with a self-reported complaint of premature ejaculation (62.5% with the lifelong form and 16.1% with the acquired form). Conversely, Lotti et al.[14] reported in an Italian study that in 244 consecutive men with couple infertility, 38 had premature ejaculation, of whom 38.5% had the lifelong form, and 61.5% had the acquired form. These frequencies were similar to those reported by Basile Fasolo et al.[81] in 2,658 Italian men with premature ejaculation admitted to an outpatient clinic for free andrological consultation (21.4% with lifelong and 69.8% with acquired premature ejaculation). In addition, in the general population, a considerably higher prevalence of acquired than lifelong premature ejaculation has been reported by studies performed in Turkey[82] (19.2% and 11.2%, respectively, in 520 men with premature ejaculation out of a cohort of 2,593 men) and in China[83] (18.8% and 12.3%, respectively, detected in 778 men with premature ejaculation out of a cohort of 3,016 men). Hence, a disparity exists between the frequency of the premature ejaculation subtypes (lifelong and acquired) in the general community and in men actively seeking treatment for premature ejaculation[84]. This result suggests that the majority of patients seeking treatment for premature ejaculation suffer from the lifelong subtype[84], whereas, in other settings, the acquired form is more frequent. The study by Lotti and colleagues[14], conducted in an infertility setting, is in line with this hypothesis[84], whereas the results from the study by Hassanzadeh and co-workers[75], performed in the same setting, give opposite results. This discrepancy could be because Hassanzadeh et al.[75] used

an unvalidated questionnaire to assess premature ejaculation, possibly identifying more men with a lifelong form because of a bias related to the diagnostic tool used, giving higher rates than those reported by Lotti et al.[14] (43% versus 15.6%). Further studies using validated tools are needed to clarify this discrepancy. Patients with acquired premature ejaculation, but not those with lifelong premature ejaculation, had a significantly higher prevalence of prostatitis-like symptoms (25% versus 1.5%; $P < 0.0001$) and colour-Doppler ultrasonography features of prostatic inflammation than patients without premature ejaculation[14]. Acquired premature ejaculation can be caused by underlying hyperthyroidism[85,86]; however, only small studies ($n = 2$–23) focusing on overt hyperthyroidism and male fertility have been performed[87], and no study has investigated the relationship between hyperthyroidism and premature ejaculation in infertile men.

A diagnosis of infertility can also lead to psychogenic anejaculation[19]. Psychogenic anejaculation can also be observed in men who do not wish to be fathers for psychological or social issues[19].

Hypoactive sexual desire disorder

Articles on the association between infertility and sexual dysfunction report hypoactive sexual desire disorder (HSDD) as a frequent factor in infertile couples[6,17–19], but they mainly focus on women's libido, whereas those investigating male sexual desire are lacking. Loss of libido in men in an infertile couple has been studied by only a few investigators, often without validated instruments (TABLE 1). In addition, no tool investigating libido has a validated cut-off value distinguishing normal sexual desire from low sexual desire, so studies often detail only self-reported feelings or comparison between infertile and control groups (TABLE 1). HSDD has been reported to be more prevalent in infertile men, with frequencies up to 45.4%[88] or 68.7%[73], than in the general population, in which its prevalence ranges from 5%[8] to 18.1%[89]. Van Zyl[73] reported an impaired sexual interest in 68.7% of men in 514 couples complaining of infertility without using any validated tool. Jain et al.[74] reported decreased libido in 11% of 175 men in infertile couples using an unvalidated tool. Ramezanzadeh et al.[88] found that 45.4% of 200 men in infertile couples reported a reduction in sexual desire after an infertility diagnosis using a self-administered structured questionnaire with a five-point rating scale assessing sexual desire and satisfaction (ranging from 1 = very unsatisfied to 5 = very satisfied). However, the authors also reported that libido did not show a considerable decrease compared with the recalled sexual desire before diagnosis[88]. A 52% frequency of HSDD in infertile men has been reported[17,18]. Bechoua et al.[19] reported that HSDD is the most frequent sexual dysfunction in infertile couples; however, this observation is limited by the fact that only studies published in French and one[29] in English were assessed in this study. Psychological pressure and loss of spontaneity, resulting from sex aimed at conception or perceived as mandatory during the ovulatory phase of the partner, was the major explanation for HSDD in this context[17–20,90]. Elia et al.[91] reported problems with sex for pleasure in 8.9% of 156 men in infertile couples and that the sexual desire of men having sex for reproductive purposes was lower than that in men having sex for pleasure or control groups, using the IIEF-5. In 2012, a study using the IIEF-15 reported that infertile men have lower sexual desire than fertile men[56]. Thus, infertile men show high rates of HSDD, with a prevalence ranging from 8.9%[91] to 68.7%[73], which is derived from studies that used unvalidated tools[73,74,88] except for one study[91].

Of note, results of one study[88] showed that sexual desire was negatively associated with duration of infertility and positively associated with coitus frequency, although in a multivariate model including the two factors as covariates, only coital frequency showed an independent association with libido. In addition, no significant difference in sexual desire between subjects with a recent (<3 months) or long-lasting (3–180 months) infertility diagnosis was observed ($P = 0.075$)[88]. Similar results were reported by others[56] using the validated tool IIEF-15 (TABLE 1). Duration of marital relationship should have been considered as a confounder, as a long relationship span is often associated with a decrease of sexual desire[88]. Hence, sexual desire is associated with coital frequency but not with duration of infertility, but the effect of duration of marital relationship should be considered in further studies.

Finally, the relationship between sexual desire and sexual arousal in infertile men is still debated. Some reports suggest that sexual arousal is maintained despite HSDD in infertile men and during infertility management[19,92,93]. However, other studies report a decrease in sexual arousal in infertile men[19,56,94]. The reduction of sexual desire in infertile couples has been related to the fact that sexual activity is focused on procreation rather than recreation and that the intrusive medical requirements affect intimacy[19,93], but results for pleasure during intercourse are discrepant and need further study.

Satisfaction and relationships

The reported associations between infertility and satisfaction (sexual or overall) are mainly based on qualitative studies[18]. In addition, the majority of the publications also analyse associations with marital relationship instability[88,95–101]. Several studies report that sexual satisfaction decreases after a diagnosis of infertility and during ART (see reviews[18,19] and TABLE 1). In particular, a low sexual satisfaction was reported after the infertility diagnosis[95–97]. Drosdzol and Skrzypulec[95] found that diagnosed male factor infertility and an infertility duration of 3–6 years were connected with the lowest sexual satisfaction by evaluating 188 infertile men using a validated Polish version of the Index of Sexual Satisfaction (ISS). Andrews et al.[96] found a weak association (R = 0.44) between male fertility-related stress and sexual dissatisfaction in 157 infertile couples using an unvalidated multiple-item scales questionnaire, but the duration of infertility was not reported. Smith et al.[97] found that those with an isolated male infertility factor showed the lowest sexual satisfaction among 357 men in infertile couples (infertility duration 1.4–2.3 years) using an unvalidated five-item sexual impact scale derived

from the Fertility Problem Inventory. Monga et al.[98] suggested that perceived male factor infertility leads to feelings of inadequacy, decreased self-esteem, and increased stress levels, which affect sexual satisfaction. A 2014 study investigating sexuality, self-esteem, and quality of the partnership[99] in 153 males of infertile couples showed that infertility is associated with reduced sexual and overall satisfaction in the relationship, self-esteem, and confidence, using the Self-Esteem and Relationship Questionnaire (SEAR). However, a prospective investigation reported no considerable changes in sexual satisfaction, evaluated using the ISS, and aspects of partnership, evaluated using the Relationship Change Scale (RCS), after infertility diagnosis[100]. The discrepancy in the results of different studies could be related to the different types of unvalidated and validated tools used to investigate this topic. Muller et al.[101] and Ramezanzadeh et al.[88] found that, on average, sexual satisfaction was high in infertile males, without a significant difference ($P = 0.08$ and $P = 0.082$, respectively) from sexual satisfaction recalled from before diagnosis.

Some studies showed no substantial group differences between sexual satisfaction in men in infertile couples and men in fertile couples[15,95], whereas others reported lower satisfaction in infertile men[56,101]. Importantly, the latter studies[56,101] evaluated smaller cohorts of infertile and fertile couples (TABLE 1); hence, they could have a low statistical power. In addition, Elia et al.[91] reported that the intercourse satisfaction of men having sex for reproductive purposes was lower than that of those having sex for pleasure or than in control groups, using the IIEF-5 (TABLE 1). Thus, the issue of sexual and overall satisfaction in infertile men is still debated, and larger systematic studies are needed to improve our understanding of this topic.

Considering factors potentially related to satisfaction in infertile couples, studies have focused on different topics, including duration of infertility, coitus frequency, timing of infertility diagnosis, cause of infertility, age of the male partner, education levels, and mutual understanding in marital life. Ramezanzadeh et al.[88] reported that duration of infertility was negatively associated with sexual satisfaction, whereas coitus frequency showed a positive correlation. However, in a multivariate model including the two factors as covariates, only coitus frequency showed an independent association with sexual satisfaction. Hence, coitus frequency was proposed as an acceptable indicator of sexual satisfaction in infertile men[88], which is in agreement with a previous study[101]. Marci and colleagues[56], using the validated IIEF-15, and Ramezanzadeh and co-workers[88], using an unvalidated tool, found no difference in sexual and overall satisfaction between men with a recent infertility diagnosis (<3 months) and those with a long-lasting (3–180 months) diagnosis of infertility. In addition, Ramezanzadeh et al.[88] also reported that the age of men in an infertile couple and the cause of infertility have no relationship with sexual satisfaction. Finally, these investigators found a significant inverse relationship between education levels or mutual understanding in marital life and sexual satisfaction (both $P < 0.05$) after a diagnosis of infertility[88]. Lee et al.[102] observed that husbands had higher sexual satisfaction than their wives in couples in which both partners were infertile. However, no differences in sexual satisfaction were observed between partners when the cause of infertility was unknown[102]. Men in couples in which the woman is infertile experienced lower global and self-esteem distress and guilt or blame than their spouses[102], whereas men in couples in which infertility was male or mixed factor or with unexplained infertility showed no differences from their female partners[102]. These results suggest that when there is a clear female contribution to the infertility status of the couple, both isolated or mixed with a male factor, women feel more guilt than men, whereas in all other instances, no differences in blame or distress between spouses are present.

Regarding the marital relationship in infertile couples, a systematic review of quantitative studies[103] concluded that male factor infertility does not negatively affect marriage. However, increased age of the infertile spouse, reduced education level, and reduced congruency of couples' perceptions of infertility were associated with worse quality of marital relationship[103]. Of note, infertile men had higher marital satisfaction than their wives[103]. These results suggest that women are more sensitive and suffer more than men in relation to the couple's infertility status, which negatively affects their marital satisfaction.

In conclusion, male factor infertility does not seem to affect dyadic relationships, but it might have a negative effect on sexual and overall satisfaction.

Orgasmic dysfunction

Orgasmic function in women in infertile couples has been widely investigated[17,18], but studies involving infertile men are limited and have been rarely performed using validated instruments (TABLE 1). Jain et al.[74] reported male orgasmic failure in 8% of 175 infertile men using an unvalidated questionnaire according to the ICD-103 (TABLE 1). Saleh et al.[60] found that 11% of 405 men undergoing infertility evaluation experienced problems with orgasm using the IIEF-15. In particular, these men failed to collect semen for a second analysis by masturbation or during sexual intercourse at home after detection of abnormalities in one or more standard semen parameters in their first semen analysis, reporting severe anxiety[60]. Elia et al.[91] reported that the orgasmic function of men having sex for reproductive purposes was lower than that of those sex for pleasure or control groups using the IIEF-5 (TABLE 1). Thus, about one in ten infertile men might experience orgasmic dysfunction.

Azoospermia and sexual dysfunction

The discovery of azoospermia can be a devastating experience for a couple during infertility evaluation[19]. This news has been described as the worst news ever received by infertile men[104] and has been associated with a deep sense of inadequacy[104]. However, the possibility of becoming a father by surgical sperm retrieval and intracytoplasmic sperm injection results in feelings of redress, enhancing self-esteem[104]. Some men experience a period of temporary erectile dysfunction after a

diagnosis of azoospermia[58,59]. A 2016 study[15] demonstrated that men with azoospermia have worse erectile function than other men who are part of an infertile or fertile couple, with a prevalence of erectile dysfunction of ~27%[15]. In addition, these men had higher frequency of premature ejaculation, lower sexual desire, and poorer orgasmic function than fertile men[15] (TABLE 1).

Azoospermia can be classified as obstructive or nonobstructive[49]. To date, only one study[105] has evaluated the effect of TESE outcome on sexual function in men with nonobstructive azoospermia. Unsuccessful TESE procedures were reported to have a negative effect on erectile function, related to hormonal and psychological issues, which was measured using the IIEF-5 (REF. 105). However, information on sexual dysfunction in men with nonobstructive azoospermia can be extrapolated from studies investigating sexual dysfunction in patients with genetic abnormalities that are often associated with nonobstructive azoospermia, such as those with Klinefelter syndrome, 46,XX testicular disorder of sexual development, or congenital hypogonadotropic hypogonadism. Raboch et al.[106] reported that the average sexual activity of 110 men with Klinefelter syndrome examined for sterility was significantly lower than that of 325 normozoospermic and potent men when measured using the Sexual Activity of Men questionnaire ($P = 0.001$). Yoshida et al.[107] found a prevalence of sexual dysfunction of 67.5% in 40 men with Klinefelter syndrome complaining of infertility (39 with azoospermia and 1 with severe oligoasthenospermia). However, men with Klinefelter syndrome showed no significant difference in the frequency of sexual dysfunction compared with a control group of 55 infertile nonazoospermic men with a normal karyotype[107]. The mean frequency of sexual intercourse per month in the patients with Klinefelter syndrome was significantly higher than in the control group ($P < 0.05$), probably because they wished to continue to have relations as a couple after the diagnosis of azoospermia[107]. Corona et al.[108] found severe erectile dysfunction in 22.7% of 23 men with Klinefelter syndrome, HSDD in 60.9% of these men, and premature or delayed ejaculation in 9.5% of these men, using a validated structured interview. However, after adjusting for confounders, the authors concluded that sexual dysfunction in men with Klinefelter syndrome was not specifically associated with the syndrome but with the underlying hypogonadal state[108], similar to the results of other studies[109]. El Bardisi et al.[110] assessed sexual dysfunction in 53 men with Klinefelter syndrome using the IIEF-5 and the Arabic index for premature ejaculation questionnaire. These investigators reported incidences of erectile dysfunction, premature ejaculation, and HSDD of 18.9%, 22.6%, and 54.7%, respectively. In addition, patients with Klinefelter syndrome had significantly lower libido and premature ejaculation frequency ($P < 0.001$ and $P < 0.05$, respectively) but similar erectile function compared with 75 age-matched men without Klinefelter syndrome[110]. Another study reported no difference in the IIEF-5 score between 86 men with nonmosaic Klinefelter syndrome and 80 men with mosaic Klinefelter syndrome[111]. The prevalence of sexual dysfunction in men diagnosed with a 46,XX karyotype undergoing fertility evaluation has been reported to be 20%[112]. Finally, untreated men with isolated hypogonadotropic hypogonadism or Kallmann syndrome are infertile owing to aspermia or azoospermia and have reduced or absent sexual activity[113].

No studies are available on sexual dysfunction in relation to obstructive azoospermia per se; however, information on sexual dysfunction in men with obstructive azoospermia can be extrapolated from studies primarily focused on patients with cystic fibrosis, as in 98% of instances they are infertile owing to obstructive azoospermia because of complete or partial agenesis of the vas deferens[114]. In these men, sexual dysfunction and difficulty in establishing intimate relationships have been reported[114]. However, these concerns were more often associated with disease-related problems than obstructive azoospermia status[114,115]. In general, sexual function is not affected until cystic fibrosis becomes severe enough to interfere with the patient's general health[116,117]. Adolescent and young adult men with cystic fibrosis are often aware that their infertility status does not affect sexual function[114,117]. However, approximately one in five men with cystic fibrosis reports that infertility affects his personal relationships[116].

In conclusion, the discovery of azoospermia in an infertility setting is associated with erectile dysfunction[15,19,58,59]. Men with azoospermia also have a higher prevalence of other sexual dysfunctions (premature ejaculation, HSSD, and orgasmic dysfunction) than fertile men[15]. Men with Klinefelter syndrome show high rates of sexual dysfunction[108,110] associated with their hypogonadal state[108,109]. They show similarerectile function to age-matched men without this syndrome, although they have a higher frequency of other sexual dysfunctions[110]. However, men with Klinefelter syndrome have worsesexual function than fertile men[106] but similar to infertile men without azoospermia in the infertility setting[107]. Overall, these data suggest a negative role for the awareness of infertility status on sexual function of men with Klinefelter syndrome. Untreated men with congenital hypogonadotropic hypogonadism have infertility and reduced sexual activity[113]. Finally, men with obstructive azoospermia owing to cystic fibrosis can develop sexual dysfunction[114] associated with the severity of the disease and disease-related problems[114–117].

Psychological disorders

The association between couple infertility and psychological burden has been widely recognized, leading the European Society of Human Reproduction and Embryology (ESHRE) to develop clinical practice guidelines[118]. These guidelines provide recommendations to improve the quality of psychosocial care for couples with infertility and during ART. The ESHRE guidelines[118] report that patients starting first-line treatments for infertility or ART do not have worse marital and sexual relationships than the general population (grade B recommendation) and that patients receiving fertility treatment do not have higher prevalence rates of sexual dysfunction than the general population (grade C recommendation)[118].

However, the ESHRE guidelines considered only one study[66] focused on the relationship between infertility, psychological burden, and sexual dysfunction, comparing it with two studies performed in the general population[8,12]. Subsequent studies have reported an association between psychological burden and sexual dysfunction in infertile men[17–19]. Infertile men can develop feelings of inadequacy, guilt, depression, distress, anxiety, low virility, low self-esteem[15,17–19,119], and psychological pressure resulting from sex aimed at conception[20,98]. Furthermore, infertility per se and related psychological problems can be associated with sexual dusfunction[15,17–19]. To date, only five studies have systematically investigated the relationship between psychopathological disorders and sexual function in men in infertile couples (TABLE 1). Shindel et al.[21] observed a significant negative relationship between premature ejaculation and self-esteem and relationship quality in 73 males in infertile couples using an unvalidated survey to assess premature ejaculation and the SEAR scale ($P = 0.02$). Lotti et al.[14] found a significant association between erectile dysfunction, which was assessed using the IIEF-15-EFD score, and depressive symptoms ($P < 0.05$), which were evaluated using the validated psychometric tool Middlesex Hospital Questionnaire (MHQ), in 244 men with couple infertility. In the same study[14], a significant association was found between the validated Premature Ejaculation Diagnostic Tool (PEDT) score and phobic anxiety ($P < 0.01$), which was evaluated using the MHQ. Gao et al.[16] found that IIEF-5 score was negatively associated with anxiety, which was evaluated using the self-rating anxiety scale (SAS), and depression, which was assessed using the self-rating depression scale (SDS) (both $P < 0.001$), whereas the PEDT score was positively associated with anxiety and depression (both $P < 0.001$) in a cohort of 1,498 infertile men. In addition, these investigators also reported a negative association between the intravaginal latency time, which was assessed using a stopwatch method, and anxiety and depression (both $P < 0.001$). Song et al.[20] observed a negative correlation between IIEF-5 score and stress level during timed intercourse, which was evaluated using a visual analogue scale. Finally, Lotti et al.[15] found that erectile dysfunction prevalence increased as a function of severity of semen quality impairment, independently of physical, hormonal, glycometabolic, or penile vascular parameters in men in fertile or infertile couples. Using a moderator analysis, these researchers[15] observed that, in infertile men, erectile dysfunction was associated with mood disturbances, particularly with somatized anxiety, and that the negative relationship between erectile function, which was evaluated with the IIEF-15-EFD score, and somatized anxiety, which was evaluated with the MHQ, was stronger in men with azoospermia ($F = 25.5$, $P < 0.0001$) than in other categories of infertile men. In addition, men with azoospermia had higher rates of premature ejaculation (which was related to overall psychopathological symptoms) and lower sexual desire and orgasmic function (which were related to depressive and somatized anxiety symptoms) than fertile men[15].

In summary, in males in infertile couples, erectile dysfunction and premature ejaculation are associated with psychological disorders, including anxiety, depression, and distress. The prevalence of erectile dysfunction increases as a function of severity of semen quality impairment, and is higher in men with azoospermia than in other men in an infertile or fertile couple[15]. Hence, investigation of sexual function and psychological status of men in infertile couples, especially if azoospermia is present, is advisable, to improve reproductive and sexual health.

Male infertility and general health

A proxy of general health

Male sexual dysfunction is a well-known index of decreased general health[22,120]. Several conditions, such as cardiovascular, glycometabolic, neurological or endocrine disorders, and cancer, as well as their treatments, such as medication, surgery, chemotherapy, and radiotherapy, might all cause organic erectile dysfunction[22]. Currently, erectile dysfunction is considered an indicator of underlying cardiovascular and metabolic disorders and as a reliable proxy of general health status[120–122]. In addition, premature ejaculation could be secondary to organic causes, such as prostatic inflammation or hyperthyroidism[123]. Furthermore, HSDD, delayed ejaculation, and orgasmic impairment might be caused by neurological and endocrine diseases, or by iatrogenic causes, including psychotropic drugs[124,125].

Male infertility has also been associated with decreased general health status[15,23,24,126–129]. In fact, men in an infertile couple have a higher rate of malignant[126–129] and nonmalignant[15,24] diseases than age-matched men without couple infertility. Accordingly, increased rates of semen abnormalities are associated with decreased general health[25,130] and increased mortality[131,132] in infertile men. Furthermore, childless men (including men with couple infertility, but also men who may have decided not to procreate) have a higher risk of dying from cardiovascular disease than men who are fathers[133]. Interestingly, subfertile males often have testosterone deficiency[33,134], which is associated with serious life-threatening conditions such as atherosclerosis, metabolic syndrome, and diabetes[134–137]. Male infertility shares particular genes and/or molecular pathways with other pathologies (such as urological and fibrous tissue neoplasms, lymphoma, myositis and dermatomyositis, and frontotemporal lobar degeneration) and has distinct clinical relationships with other diseases (including testicular and high-grade prostate cancer)[138].

Lotti et al.[15] observed that men with azoospermia had the highest frequency of erectile dysfunction and the worst health status in an evaluation of men in infertile and fertile couples (TABLE 1). Furthermore, erectile dysfunction was associated with decreased health status only in men with azoospermia. The investigators suggested that the presence of erectile dysfunction in infertile men, particularly men with azoospermia, might prompt physicians to evaluate possible subclinical underlying morbidities. An early diagnosis of erectile dysfunction and the identification of its risk factors can provide useful information for eventually stratifying cardiovascular risk[26,27,121,139,140]. Whether or not erectile

dysfunction in infertile men might be an earlier marker of cardiovascular diseases needs further investigation. A 2017 study reported an association between failure in fertility therapy and an increased risk of long-term adverse cardiovascular events in women[141]; however, such studies are lacking in infertile men. Together, these observations show that the concept that erectile dysfunction in infertile men might be an early marker of poor general health is emerging.

General health disorders

The aetiologies of impaired sperm production, function, or release can be related to different congenital or acquired conditions that act at a pretesticular level (such as congenital or acquired hypogonadotropic hypogonadism and sexual dysfunction), a post-testicular level (such as congenital bilateral absence of vas deferens, ejaculatory duct obstruction caused by a congenital midline prostate cyst or acquired after prostate infection or inflammation, vasectomy, and antisperm antibodies), or directly at the testicular (such as congenital anorchia, karyotype abnormalities, and Y chromosome deletions and acquired causes such as orchitis, testicular torsion, trauma, irradiation, and chemotherapy) level[14,28,34–36]. Among these disorders, systemic diseases (such as chronic renal or liver failure, and respiratory, neurological, and endocrine diseases) have been reported as individual disorders in 2.2% of a large cohort of patients attending the Münster Institute of Reproductive Medicine[34] and in 0.5% of a subgroup of 1,446 men with azoospermia. A 2017 study[35] indicates that chronic diseases (including cardiovascular, renal, gastrointestinal, joint, neurological and endocrine diseases, asthma, and depression) contributed to severe male factor infertility in 24.4% of 1,737 men, showing a significantly higher prevalence than in 325 fertile men (9.8%) ($P < 0.001$).

Systemic diseases can affect semen parameters[23] and male sexual function[22], as they often share common pathological mechanisms (TABLE 2). Systemic diseases can cause disruption of the hypothalamic–pituitary–gonadal (HPG) axis[23], leading to testosterone deficiency[23,33], which, in turn, can eventually result in erectile dysfunction, HSDD, and delayed ejaculation[85,142]. The mechanism related to defective HPG axis regulation is called ontogenic regression and refers to the orderly regression of reproductive function in a fashion that permits facile recrudescence when a more favourable environment prevails[23]. Along with disruption of the HPG axis, other common features of systemic illness, such as increased cytokine levels, fever, weight loss, and increased catabolism can all reduce testicular function[23].

The negative reproductive and sexual effects of non-testicular illnesses depend on age as well as how severe and chronic the underlying disease is[23,143,144]. Acute and chronic illnesses are often associated with suppression of gonadotropin secretion and secondary hypogonadism, but primary hypogonadism can also occur[23,144]. Notably, about 20% of all children have a chronic illness that often leads to growth failure and delay or absence of sexual development during puberty and to subfertility and sexual dysfunction during adolescence and early adulthood[143]. This observation is relevant because many studies indicate that adolescents and young adults are sexually active and interested in knowing about their future fertility[143]. Furthermore, reproductive and sexual impairment can affect the future quality of life of these patients and are predictors of stress in current and future relationships[143].

Thus, causes of semen abnormalities and sexual dysfunction are multifactorial and can be caused by the disease itself and its associated complications[143]. Adequate information must be provided to patients about reproductive and sexual health, and transitional care between paediatric and adult medical care should be improved[143].

Medical treatments

Male infertility treatments

Male infertility treatments include therapeutic strategies aimed at treating both correctable and idiopathic causes of infertility. Correctable causes of infertility include hypogonadotropic hypogonadism and other endocrine disorders, varicocele, and sexual problems (erectile dysfunction and other ejaculatory disorders).

Hypogonadotropic hypogonadism. Treatment of hypogonadotropic hypogonadism in infertile men includes selective oestrogen receptor modulators, gonadotropins and, less frequently, aromatase inhibitors, which can restore serum testosterone levels, providing symptomatic relief without affecting sperm production[145–147]. Conversely, exogenous testosterone, a medication known for its contraceptive potential, should not be used for male infertility treatment[145–147]. Several studies have evaluated the effect of the aforementioned medications on testosterone levels in hypogonadal men of reproductive age[145–147], but only a few evaluated their effect on sexual function[148,149], and no study had evaluated this issue in infertile men. Guay et al.[148] demonstrated that treatment with clomiphene citrate for 4 months in 173 men with secondary hypogonadism and erectile dysfunction was associated with an improvement in sexual function in 75% of men, probably by increasing luteinizing hormone and free testosterone levels. Similar results were observed in a smaller cohort ($n = 17$), in a subgroup of eight men with a mean age of 53 years who were younger than the rest of the sample ($n = 9$, mean age 66.4 years), and in those with fewer medical risk factors, including diabetes and hypertension ($n = 8$)[149]. Responses to treatment significantly decreased as a function of age ($P < 0.05$), concomitant diseases (hypertension and coronary artery disease; both $P < 0.05$), or use of multiple medications ($P < 0.05$)[148]. Similarly, other studies reported a significant improvement in the Androgen Deficiency in Ageing Male sexual function domain score in hypogonadal men receiving clomiphene citrate treatment (all $P < 0.05$)[150–152]. Finally, a placebo-controlled study performed in a small cohort ($n = 45$) of men with nonorganic erectile dysfunction or HSDD with normal (>4 ng/ml) or slightly decreased (2–4 ng/ml) testosterone levels indicated that human chorionic gonadotropin (hCG) treatment was associated with an improvement in sexual behaviour in ~50% of the cases[153].

Table 2 | **Systemic diseases that might lead to semen abnormalities and sexual dysfunction**

Systemic diseases	Semen abnormalities and sexual dysfunctions and possible underlying mechanisms
Renal diseases	
Chronic renal failure	• Frequent testosterone deficiency owing to hypogonadotropic hypogonadism and testicular damage • Inhibition of HPG axis: hypogonadotropic hypogonadism, with gonadotropin levels inappropriately low for the low testosterone levels; however, masked by reduced clearance related to uraemia, which can lead to apparently high gonadotropin levels[23] • Luteinizing hormone insensitivity of Leydig cells[23] • Increased testosterone clearance[23] • Impaired spermatogenesis, including azoospermia, and low semen volume[177] • Possible cytotoxic effect of uraemia on spermatogonia[23] • High rates of sexual dysfunction (mainly erectile dysfunction and HSDD) related to testosterone deficiency, uraemia, fatigue, and psychosocial factors[22,178]
Dialysis and renal transplantation	• Dialysis is associated with testosterone deficiency[23], sperm abnormalities[177], and sexual dysfunction[178]; however, better than end-stage renal disease[177] • Renal transplantation restores testicular function, spermatogenesis[177], and erectile function[22]
Liver diseases	
Chronic liver failure	• Increase in SHBG levels and decrease of bioavailable testosterone; gonadotropin in the low-to-normal range; additional direct testicular damage from alcohol in alcohol-related forms of the disease[23] • Impaired HPG axis and hypogonadotropic hypogonadism in cirrhosis and increased peripheral conversion of androgens to oestrogens[179] • Sperm abnormalities, including azoospermia[23]; antisperm antibodies in alcohol-related forms of the disease[180] • Erectile dysfunction[181] and HSDD[181]
Liver transplantation	• Improvement in testosterone levels, erectile function[181], and sperm parameters[23] with respect to end-stage liver disease; however, mild-to-moderate sexual dysfunction might persist[182]
Haemochromatosis	• Iron deposition in pituitary gland and testes[179] with frequent hypogonadotropic hypogonadism, rarely reversed by iron desaturation[23] • Sperm abnormalities[23] • Sexual dysfunction[183] • Iron deposition in liver and pancreas can lead to cirrhosis and diabetes, respectively[23], with further negative effects on sexual and reproductive health
Respiratory diseases	
Cystic fibrosis	• 98% of men with cystic fibrosis have congenital bilateral absence of vas deferens and obstructive azoospermia[114] • Men with cystic fibrosis can develop sexual dysfunction[114] related to the severity of the disease and related problems[114–117]
Sarcoidosis	• 50% of men with sarcoidosis show hypogonadotropic hypogonadism[23] • Neural involvement in 5% of men with sarcoidosis (neurosarcoidosis) can produce hypogonadotropic hypogonadism by pituitary infiltration[23] • Sperm abnormalities, including azoospermia, improving with corticosteroid therapy[23] • Sexual dysfunction[184]
Chronic obstructive pulmonary disease	• Testosterone deficiency owing to primary illness and glucocorticoid therapy[185] • Supposed effect on male reproductive function, but debated[23] • Erectile dysfunction[22]
Genetic neurological disorders	
Myotonic dystrophy	• Compensated or hypergonadotropic hypogonadism[186] • Sperm abnormalities, including azoospermia[187] • 25% of men with myotonic dystrophy have erectile dysfunction[186]
Kennedy disease	• Testosterone deficiency[188] • Sperm abnormalities[188,189] and sexual dysfunction[189]
Acquired neurological disorders	
Multiple sclerosis	• 25% of men with multiple sclerosis have testosterone deficiency[23] • Spermatogenesis impaired according to authors[46], not impaired for other authors[23], but infertility might occur when erectile dysfunction and/or ejaculatory disorders are present[23] • Sexual dysfunction, including erectile dysfunction, HSDD, ejaculatory disorders, and orgasmic dysfunction[22]
Polyneuropathy	• Erectile dysfunction and ejaculatory disorders[22] can lead to infertility
Spinal cord injury	• Spinal cord injury is the most common cause of neurogenic anejaculation[45]. • Only 9% of men with spinal cord injury can achieve ejaculation via masturbation or sexual intercourse[46] • 50–75% of men with spinal cord injury have erectile dysfunction[190]
Epilepsy	• Testosterone deficiency, erectile dysfunction, and HSDD[22] • Semen parameters mildly affected[191]
Head injury	• Partial or complete pituitary dysfunction, including hypogonadotropic hypogonadism[23], leading to sperm abnormalities and sexual dysfunction

Table 2 (cont.) | **Systemic diseases that might lead to semen abnormalities and sexual dysfunction**

Systemic diseases	Semen abnormalities and sexual dysfunctions and possible underlying mechanisms
Acquired neurological disorders (cont.)	
Pituitary adenoma	• Hypogonadotropic hypogonadism for macroadenoma affecting gonadotropins by pituitary compression against sella turcica, or possible hormonal hypersecretion (prolactin, ACTH, and growth hormone) owing to pituitary adenoma finally affecting the HPG axis[192], leading to sperm abnormalities and sexual dysfunction
Gastrointestinal diseases	
Coeliac disease	• Testosterone deficiency[193] • Sperm abnormalities[194] • Sexual dysfunction[195]
Inflammatory bowel diseases	• Testosterone deficiency, debated[23] • Impaired spermatogenesis[196]; increased levels of antisperm antibodies[197] • Sexual dysfunction[195]
Haematological diseases	
β-Thalassemia	• Hypogonadotropic hypogonadism and impaired spermatogenesis[198] • Erectile dysfunction[199]
Sickle cell disease	• Testosterone deficiency, sperm abnormalities, and erectile dysfunction, also related to complicated priapism[200]
Endocrine and metabolic diseases	
Hyperprolactinaemia	• HPG axis suppression and hypogonadotropic hypogonadism; sexual dysfunction, including erectile dysfunction and HSDD, owing to secondary testosterone deficiency and direct negative effect of prolactin levels on sexual desire[85] • Semen abnormalities[201]
Hyperthyroidism	• Increased SHBG and decreased bioavailable testosterone levels[87] • Sperm abnormalities[86,87] • Erectile dysfunction and premature ejaculation[85]
Hypothyroidism	• Decreased SHBG and testosterone levels[87] • Semen abnormalities[86,87] • Erectile dysfunction and delayed ejaculation[85]
Hypercortisolism	• Inhibition of HPG axis and hypogonadotropic hypogonadism; possible effect on reproductive and sexual function[202]
Acromegaly	• Hypogonadotropic hypogonadism and sperm abnormalities (also caused by an excess of growth hormone)[203,204] • Erectile dysfunction, mainly organic[204]
Congenital adrenal hyperplasia	• Sperm abnormalities owing to hypogonadotropic hypogonadism, testicular failure, and testicular adrenal rest tumours[205] • Sexual dysfunction[206]
Diabetes mellitus	• Hypogonadotropic hypogonadism[207] • Semen abnormalities and ejaculatory disorders, including retrograde ejaculation[43] • Erectile dysfunction[22]
Obesity	• Hypogonadotropic hypogonadism[208] • Reduced reproductive potential[209], but sperm abnormalities are debated[210,211] • Erectile dysfunction[22]
Metabolic syndrome	• Hypogonadism owing to central and testicular function impairment[212] • Men with metabolic syndrome show lower values of normal sperm morphology than those without[122]. In men with primary couple infertility, no difference in semen parameters have been reported when comparing men with and without metabolic syndrome[136]. In men with secondary couple infertility, patients with metabolic syndrome showed lower values of semen volume, sperm concentration, and normal morphology than those without[137] • Erectile dysfunction[22]
Autoimmune rheumatic diseases	
Autoimmune rheumatic diseases in general	• Sexual dysfunction owing to disease-related symptoms (pain, fatigue, functional impairment, and psychological disturbances), hypogonadism, and impaired fertility owing to increased levels of antisperm antibodies and testosterone deficiency in rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis[213]
Infectious diseases	
HIV	• Testosterone deficiency[214] • Semen abnormalities[215] • Erectile dysfunction in 30–50% of men with HIV[216]
Sexually transmitted infections	• Possible negative effect on semen parameters; however, this issue and effects on fertility are debated[200] • Erectile dysfunction and premature ejaculation in urogenital infections[217]
Human papilloma virus	• Some evidence for HPV as a risk factor for fertility, with possible negative effects on semen quality, IVF failure, and miscarriages, but its influence is debated, as is the role of HPV clearance in restoring fertility[218] • Risk factors for HPV infection in both sexes are number of lifetime partners and young age[219,220] • Women with vulvar lesions more often worry about sexual consequences (such as being unable to have children, being sexually less attractive, or infecting a sexual partner) than those without[221]. • Men with genital warts have higher rates of sexual dysfunction, depression, and anxiety than the general population[222]

Table 2 (cont.) | **Systemic diseases that might lead to semen abnormalities and sexual dysfunction**

Systemic diseases	Semen abnormalities and sexual dysfunctions and possible underlying mechanisms
Infectious diseases (cont.)	
Male accessory gland infection	• Possible negative effect on semen parameters[223]; effect on fertility debated[215] • Sexual dysfunction (erectile dysfunction, premature ejaculation, or HSDD) in up to 50% of men[224]
Mumps	• 15–30% of adult men develop epididymo-orchitis, with sperm abnormalities in up to 25% of patients, and normal or decreased testosterone levels[225], which might lead to sexual dysfunction[226]
Lepromatous leprosy	• Possible testicular and epididymal abnormalities, with sperm abnormalities[227] • Sexual dysfunction in up to 60% of men[227] • Testosterone deficiency might occur[228]
Cardiovascular diseases	
Cardiovascular diseases in general	• Testosterone deficiency[229] • Sperm abnormalities[130,135] • Erectile dysfunction[22]
Malignancy	
Malignancy	• Sperm abnormalities and testosterone deficiency owing to ontogenic regression (fever, weight loss, cytokines, chemotherapy, and radiotherapy)[23] • Sexual dysfunction[230]
Other diseases	
Psoriasis	• Impaired spermatogenesis[231] • Erectile dysfunction[232]
Amyloidosis	• Hypogonadism owing to testicular amyloid deposition[233] • Semen abnormalities[233] • Erectile dysfunction in amyloid neuropathy[234]
Behçet disease	• Genitourinary inflammation and recurrent fever affect spermatogenesis[235] • Sexual dysfunction[236]

ACTH; adrenocorticotropic hormone; HPG, hypothalamus–pituitary–gonadal; HPV, human papilloma virus; HSDD, hypoactive sexual desire disorder; IVF, in vitro fertilization; SHBG, sex-hormone-binding globulin.

Other endocrine and metabolic disorders. Other endocrine and metabolic disorders potentially related to abnormal semen parameters and sexual dysfunction include hyperprolactinaemia, hyperthyroidism and hypothyroidism, congenital adrenal hyperplasia, acromegaly, hypercortisolism, diabetes mellitus, metabolic syndrome, and obesity (TABLE 2). Treatment of these disorders can result in normalization of semen parameters and sexual function[85,86,154].

Varicocele. Varicocele is considered as an aetiological factor in male infertility[28,35,155]. Varicocele is often associated with a reduction in serum testosterone levels, and varicocelectomy can reverse some of the adverse effects of androgen deficiency, including sexual dysfunction[156,157]. A few studies have found an association between varicocele and sexual dysfunction. One study reported an association between varicocele and premature ejaculation, likely owing to varicocele-related congestion of the periprostatic venous plexus and prostate inflammation[158]. Varicocelectomy has been associated with improvement in premature ejaculation[159,160]. However, further prospective studies with larger patient groups are needed to confirm this finding[161]. Furthermore, in a large population-based case-control study, a higher prevalence of varicocele has been observed in participants with erectile dysfunction than those without[162]. Varicocelectomy has been associated with an improvement in IIEF-5 score in infertile men with hypogonadism (baseline total testosterone levels <300 ng/dl), probably related to an increase in testosterone levels after surgery[163]. Finally, 34–67% of men with varicocele and infertility reported HSDD[158,163], and HSSD was attributed to a varicocele-induced decline in testosterone levels[163]. However, the possibility that infertility per se causes HSDD should also be considered[156].

Idiopathic male infertility. Regarding idiopathic male infertility, a survey of practising American Urological Association members[164] evaluating treatments used by 347 urologists found that 60.5% would treat infertile men with empirical therapy for 3–6 months, mainly using clomiphene citrate and hCG, but also testosterone (25%), which can have deleterious effects on sperm production. Comparing fellowship-trained and general urologists, the latter group showed a significantly higher use of testosterone ($P=0.001$) and a lower use of hCG or anastrazole (both $P<0.001$)[164]. These findings highlight the need to establish recommendations on the empirical use of medical therapy in the setting of male infertility[164], and to transfer this knowledge, especially to the general urologists.

Assisted reproductive technologies. ARTs can lead to sexual dysfunction[19,165]. ARTs are the infertility treatments of choice for couples unable to obtain natural pregnancy[166]. A 2014 survey by the Italian Society of Andrology and Sexual Medicine[167] demonstrated that men undergoing ART often have erectile dysfunction

(56.2%), premature ejaculation (25%), or HSDD (18.7%). The reasons for the development of sexual dysfunction in this setting include partner, couple and clinical team expectation of ART success, leading to anxiety and distress, the sex for the reproduction process itself, and the need to provide one or more semen samples on demand using masturbation[17–19,165]. Long periods of diagnostic and treatment procedures can have a detrimental role in sexual life[168]. However, only a few studies have evaluated the relative effect of the duration of infertility, of the related work-up, and of treatment on male sexual function and marital relationship[65,88,95,169] but not with these factors as a primary end point and without definitive results. One study reported that a 3-month treatment with clomiphene citrate of female partners of men with primary infertility performed before intrauterine insemination was associated with an increase of sexual dysfunction frequency in both members of the couple[169]. In particular, men showed reduced sexual drive, arousal, orgasm intensity, and satisfaction compared with those observed before treatment, as assessed with the Arizona Sexual Experience Scale[169]. Another study[88] reported that, when comparing infertile men diagnosed and treated recently (within 3 months) to those managed for a longer period (3–180 months), those men treated for longer had reduced sexual satisfaction; however, sexual satisfaction was not different from that recalled before diagnosis. The size of the recently diagnosed group was too small ($n = 12$) to draw conclusions, and larger studies are advisable[88]. Another study found no association between duration of infertility and IIEF-15 subdomain score[65], whereas another found a higher rate of marital conflicts in couples with a duration of 3–6 years of infertility problems than those with a longer or shorter duration[95]. Thus, further research on this topic is warranted. Finally, masturbation is considered as an immoral practice in some cultures and religions, and is perceived with guilt by some patients undergoing ART, possibly leading to psychogenic erectile dysfunction or anejaculation[19].

In summary, the treatment of correctable causes of infertility in men with sexual dysfunction can lead to improvement of both semen parameters and of sexual function. In particular, the treatment of men with hypogonadotropic hypogonadism and sexual dysfunction with clomiphene citrate is associated with an improvement in sexual function[148–152], probably owing to an increase in testosterone levels[148]. These results are from studies performed in men without infertility, but they can be extended to an infertility setting. In fact, clomiphene citrate, as well as hCG, are often used as empirical therapies for idiopathic male infertility[164]. However, testosterone is also frequently used (wrongly) in the infertility setting, although it should be avoided in men seeking pregnancy because of its contraceptive potential[164]. Treatment of some endocrine and metabolic disorders in men with semen abnormalities can result in an improvement of semen parameters and sexual function[85,86,154]. One study[163] reported that varicocelectomy is associated with an improvement in erectile function in infertile men with hypogonadism. Evaluation and assisted treatment (ART) of infertility is an important risk factor for sexual dysfunction[165,167,168].

Medication and infertility

Increasingly, young men (aged <40–45 years) require long-term medication (such as chemotherapy for tumours, psychotropic agents for psychological or psychiatric disorders, and testosterone replacement therapy for hypogonadism secondary to obesity, diabetes, or metabolic syndrome), of which the effects on reproduction and sexuality are often inadequately considered[170]. Medication can affect male reproduction through central suppression of the HPG axis, direct gonadotoxic effects, reducing semen quality, or inducing sexual dysfunction[33,170]. In particular, sexual dysfunction has commonly been reported as an adverse effect of many drugs (such as psychotropic agents for psychological or psychiatric disorders, some antihypertensive medications for hypertension, 5α-reductase inhibitors for male pattern baldness and benign prostatic hyperplasia, and α-blockers for lower urinary tract symptoms or benign prostatic hyperplasia)[171,172]. Many medications have reversible effects on male fertility, but some of them, such as chemotherapeutic agents, can lead to irreversible infertility and, eventually, decreased testosterone production (TABLE 3). Men should be counselled appropriately about potential drug-related adverse effects on their fertility and sexual function.

Sexual dysfunction in couple infertility

Sexual dysfunction in men in an infertile couple can be the cause or the consequence of the infertility status or might be present independently. When sexual dysfunction is independent of the infertility status, the cause must be investigated, and treatment must be performed according to available guidelines of the EAU[173] and of the International Society of Sexual Medicine[174,175], avoiding use of those medications affecting fertility if possible (TABLE 3). When the possible underlying cause of both sexual dysfunction and infertility is recognized, such as a systemic disorder (BOX 1; TABLE 2) or ongoing medication (TABLE 3), the condition must be treated or the medication discontinued or changed to a suitable alternative. Patients should be monitored in order to evaluate any possible improvement. Of note, several systemic disorders are associated with hypogonadism (TABLE 2). If hypogonadism is present in a man seeking infertility treatment, testosterone replacement therapy (TRT) must be avoided and other medications considered (such as hCG, selective oestrogen receptor modulators, or aromatase inhibitors), as TRT can further reduce semen quality[145–147]. Anejaculation can be treated with psychotherapy or medication when caused by a psychogenic or marital issue[174,176]. However, when anejaculation is resistant to treatment or not correctable (such as when it is secondary to severe organic or iatrogenic causes; BOX 1), only fertility can be treated by performing TESE and ART. Regarding HSDD, orgasmic dysfunction, and satisfaction impairment, medical and/or psychological therapy can be performed[174–176], possibly avoiding medications that would worsen subfertility.

Table 3 | **Commonly used medications and semen abnormalities and sexual dysfunction**

Commonly used medications	Semen abnormalities	Mechanisms leading to semen abnormalities[a]	Sexual dysfunctions	Mechanisms leading to sexual dysfunctions[a]
Hormone therapy				
Testosterone	Impaired spermatogenesis[170]	Suppression of the HPG axis	Amelioration of sexual function[142]	Central and peripheral effect
BPH treatments				
α-Blockers	• Retrograde ejaculation[237] • Decreased semen volume[237] • Reduced sperm count and motility[237]	• Inhibition of bladder neck α_{1A} receptors • Inhibition of vas deferens and epididymal α_{1A} receptors and reduced contractility	HSDD or erectile dysfunction with tamsulosin[238]	Unknown
5α-Reductase inhibitors	• Decreased sperm count in 5% of men[239] • Decreased semen volume[239]	Block testosterone-to-DHT conversion	• HSDD • Erectile dysfunction up to 15% of men[240]	Alterations in neurosteroid levels in the cerebrospinal fluid
Psychotropic medications				
Psychotropic medications in general	NA	NA	NA	Serotoninergic, anticholinergic, α-blocker, and/or antidopaminergic properties
SSRIs	• Increased sperm DNA fragmentation[241] • Direct spermicidal effect (in vitro)[241] • Decreased sperm motility[241]	• Oxidative phosphorylation of sperm mitochondria or effect on the sperm cell membrane • Hyperprolactinaemia with suppression of the HPG axis	• Erectile dysfunction (up to 60% of men)[242] • Delayed or absent ejaculation (variable degree)[242]	• Hyperprolactinaemia, with suppression of the HPG axis • Impaired binding of luteinizing hormone to Leydig cells • Sedative properties
Tricyclic antidepressants	• Decreased sperm motility[243] • Decreased semen volume[243]	Hyperprolactinaemia with suppression of the HPG axis	Erectile dysfunction and delayed or absent ejaculation (variable degree) with phenothiazines[242]	Hyperprolactinaemia with suppression of the HPG axis
MAO inhibitors	Azoospermia with anejaculation[244]	Blocks the enzyme MAO, which normally inactivates the monoamines serotonin, dopamine, and noradrenaline	• HSDD[244] • Erectile dysfunction[244] • Anejaculation[244]	Blocks the enzyme MAO, which normally inactivates the monoamines serotonin, dopamine, and noradrenaline
Lithium	Decreased sperm motility[243]	Unknown	• HSDD[244] • Erectile dysfunction[244]	Decrease in central nervous system dopamine levels
Antihypertensive medications				
β-Blockers	Decreased sperm motility (in vitro)[245]	Unknown	• HSDD[246] • Erectile dysfunction[246]	Central (amygdala and cerebral cortex) and penile (sympatholytic effect) β1-adrenergic receptor inhibition
Diuretics	Decreased sperm concentration and motility (spironolactone)[247]	Unknown	HSDD and erectile dysfunction (spironolactone and clortalidone)[248]	• Antiandrogenic effect (spironolactone) • Sympatholytic effect (hydroclorothiazide)
Phosphodiesterase inhibitors				
Phosphodiesterase inhibitors in general	• No change or improvement in conventional sperm parameters[170] • One report of sperm motility decrease with acute tadalafil use[249]	Phosphodiesterases are expressed in human sperm, Leydig cells, and several organs of the male genital tract	Improve sexual function[170]	Phosphodiesterases expressed in several organs; phosphodiesterase type 5 in the penis is the target of phosphodiesterase type 5 inhibitors
Anticancer medications				
Chemotherapeutic agents	• Azoospermia or reduction in conventional sperm parameters[170] • Sperm DNA fragmentation[170] • Sperm aneuploidy for up to 2 years[170]	• Gonadotoxicity from damage to Sertoli or Leydig cells and spermatogonial stem cells; risk of genetically abnormal sperm precursors • Alkylating agents produce covalent bonds between DNA strands and block cell division	• HSDD[230] • Erectile dysfunction[230]	Decrease in testosterone production by damage to Leydig cells; fatigue, pain, or anxiety about therapy

Table 3 (cont.) | **Commonly used medications and semen abnormalities and sexual dysfunction**

Commonly used medications	Semen abnormalities	Mechanisms leading to semen abnormalities[a]	Sexual dysfunctions	Mechanisms leading to sexual dysfunctions[a]
Immunosuppressive drugs				
Sulfasalazine	Reduction in conventional sperm parameters, induction of azoospermia[250]	Negative effect on spermatozoa of the sulfapyridine metabolite of sulfasalazine[250]	Rare reports of erectile dysfunction[251]	Unknown
Methotrexate	Reduction in conventional sperm parameters, induction of azoospermia[251]	Gonadotoxicity and chromosomal defects	Rare reports of sexual dysfunction[251]	Unknown
Antiepileptic drugs				
Carbamazepine and other enzyme-inducing drugs; valproate	Reduction in conventional sperm parameters[252]	Increase of SHBG and reduction of bioavailable testosterone levels	• HSDD[252] • Erectile dysfunction[252]	Increase of SHBG and reduction of bioavailable testosterone levels

DHT, dihydrotestosterone; HPG, hypothalamus–pituitary–gonadal; HSDD, hypoactive sexual desire disorder; MAO, monoamine oxidase; NA, not applicable; SHBG, sex-hormone-binding globulin; SSRI, selective serotonin reuptake inhibitor. [a]See REFS 170,213,251,252.

Conclusions

Sexual dysfunction is a rare cause of male infertility; however, every type of sexual dysfunction has been observed in infertile men. In fact, one out of six men in an infertile couple has erectile dysfunction or premature ejaculation, whereas orgasmic dysfunction is estimated to be present in one out of ten infertile men. HSDD and lack of satisfaction in sexual life are the most prevalent types of sexual dysfunction in infertile men. The infertility status and its related psychological concerns can underlie sexual dysfunction.

General health perturbations can lead to male infertility and/or sexual dysfunction. Indeed, erectile dysfunction and male infertility are considered proxies of general health. Furthermore, the concept that erectile dysfunction in infertile men might be an early marker of poor general health is emerging. Men with azoospermia show the highest rates of psychological and general health disturbances, which are associated with an increased prevalence of sexual dysfunction. Finally, commonly used medications for general health problems can lead to sperm abnormalities and sexual dysfunction, and, therefore, adequate information must be provided to patients. Preliminary evidence indicates that the treatment of some correctable causes of male infertility can improve semen quality and reverse infertility-related sexual dysfunction. Investigation of sexual function, general health, and psychological status of men in an infertile couple, especially if they have azoospermia, is advisable, to improve reproductive, general, and sexual health.

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