






Sexual dysfunctions in male patients with infertility: recommendations from the Fifth International Consultation for Sexual Medicine (ICSM 2024)

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Abstract

Introduction: The issue of sexual dysfunction in infertile couples is often neglected and underreported. As sexual dysfunction can both contribute to and result from infertility, clinicians should be equipped to identify and address these issues as part of comprehensive fertility care.

Objectives: To develop evidence- and consensus-based recommendations for the clinical management of male sexual dysfunction (MSD) in the context of infertility.

Methods: Initial recommendations were formulated based on expert opinion and exploratory analysis of various types of MSD associated with infertility. A focused literature review was conducted for each topic, followed by iterative rounds of expert discussion to refine recommendations. Final consensus was achieved at the 5th International Consultation on Sexual Medicine meeting, and recommendations were rated using GRADE criteria.

Results: MSD and infertility often coexist, necessitating a detailed sexual history and physical examination during the initial infertility evaluation. Erectile dysfunction may be effectively managed with counseling, phosphodiesterase-5 inhibitors, or intracavernosal injections (eg, alprostadil, papaverine, phentolamine), which do not impair fertility outcomes. For low libido or unconsummated marriages, a multidisciplinary approach tailored to the couple's priorities—sexual function or fertility—is recommended. Ejaculatory disorders may be treated with counseling, penile vibratory stimulation, electro-ejaculation, medications, or assisted reproduction, depending upon the underlying cause. Selective serotonin reuptake inhibitors, used for premature ejaculation, may adversely affect sperm parameters and should be prescribed cautiously. Men with hypogonadism seeking fertility should avoid exogenous testosterone; alternatives such as selective estrogen receptor modulators, aromatase inhibitors, or gonadotropins may be considered. Lifestyle optimization, management of comorbidities, and use of fertility-safe lubricants can improve sexual and reproductive outcomes for couples trying to conceive.

Conclusion: MSD and infertility are often interrelated. Incorporating routine sexual health assessments into fertility evaluations enables clinicians to diagnose and treat MSD effectively, thereby improving both sexual function and reproductive success.

Keywords: male infertility; sexual dysfunction; hypogonadism; erectile dysfunction; ejaculatory dysfunction; lifestyle modifications.

Introduction

Infertility is a global problem affecting around 10% of couples¹ and 12% of men.² Sexual disorders are often observed in infertile couples.³ Varying prevalence rates (17.8%–61.6%) of sexual dysfunction (SD) in infertile men have been reported.⁴

Male sexual dysfunction (MSD) may be the cause of infertility, or infertility treatment may precipitate sexual dysfunction. The management of MSD in infertile couples is often neglected while the reproductive management of the female is prioritized. Despite the role of sexual health as an overall

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Recommendations

1.	Sexual dysfunction and infertility frequently co-exist, as either cause or effect of the other, and hence evaluation of an infertile couple should include a detailed sexual history and physical examination.	Grade of recommendation: Strong
2.	Situational ED in couples trying to conceive can be minimized through appropriate counseling and/or medication.	Grade of recommendation: Weak
3.	Oral phosphodiesterase 5 inhibitors can be safely used by couples attempting to conceive.	Grade of recommendation: Strong
4.	Infertile men with situational erectile dysfunction, who are non-responsive to oral phosphodiesterase 5 inhibitors, can be offered self-administered intra-cavernosal injection therapy.	Grade of recommendation: Weak
5.	Infertility due to an unconsummated marriage is common in some societies and presents a complex problem that should be treated by a multidisciplinary team, addressing both male and female factors simultaneously, with a priority on fertility or sexual function as per the couple's goals.	Grade of recommendation: Strong
6.	Low male libido, resulting in infrequent intercourse, can be the primary cause of infertility and should be treated with a multidisciplinary approach, since the etiology can be varied.	Strength of recommendation: Strong
7.	Premature ejaculation can be a cause of infertility if there is consistently ejaculation prior to penetration. However, medical therapy to treat this should be prescribed with caution as these medications may impair sperm quality.	Grade of recommendation: Weak
8.	Persistent anejaculation (orgasmic or anorgasmic), characterized by the complete absence of an antegrade ejaculate, or severely delayed ejaculation leading to repeated failure to deposit semen intravaginally, will result in infertility.	(Expert opinion)
8A.	Anorgasmic Anejaculation and Delayed Ejaculation are usually due to psychological or physiological causes but occasionally may have an organic etiology. In non-neurogenic cases, psycho-sexual therapy or vibrator-assisted orgasm may resolve the problem and allow natural conception. Otherwise, assisted reproduction using sperm obtained by masturbation, vibratory stimulation, electro-ejaculation or surgical retrieval would be required.	Grade of recommendation: Strong
8B.	Orgasmic anejaculation (reaching orgasm without ejaculation) is due to an organic cause (anatomic obstruction of ejaculatory and prostatic ducts, neurogenic damage, medication, or severe hypogonadism); it may be treated by medical therapy, penile vibratory stimulation, electro-ejaculation, or sperm retrieval and assisted reproductive technology.	Grade of recommendation: Strong
9.	Men with symptomatic hypogonadism who are interested in fertility should not be treated with exogenous testosterone replacement and instead may be treated with selective estrogen-receptor modulators, aromatase inhibitors, or gonadotropins, which will increase testosterone while maintaining fertility.	Strength of recommendation: Strong
10.	Couples attempting to conceive may use lubrication, if needed, and should be advised to use sperm-safe lubricants.	Grade of recommendation: Strong
11.	Optimization of comorbid conditions/illness and appropriate lifestyle changes may improve both sexual and reproductive health.	Grade of recommendation: Strong

marker of general health,^{5,6} sexual medicine is not routinely taught during medical school and residency training.⁷ Hence, there is reluctance, even from fertility doctors, to discuss the management of sexual problems.

The purpose of these guidelines is to identify the various kinds of MSD that can be associated with infertility and to provide evidence-based recommendations and expert opinion on the management of these problems (Figure 1).

Methods

An initial exploratory analysis was conducted to identify various subtopics pertaining to MSD that may be seen in association with infertility. These were formulated into provisional recommendations based on expert opinion. Multiple literature searches, relevant to each subtopic, were then performed using Medline and PubMed databases, up to June 2024, to identify pertinent studies, which were then carefully reviewed to create summaries of the available evidence. These were used to reframe the initial recommendations. The modified recommendations were then subjected to multiple rounds of revision, using a modified Delphi process⁸ until a consensus was reached amongst all members and a final list of recommendations was prepared. These were further discussed and revised at the 5th International Consultation on Sexual Medicine (Madrid, June 2024). The recommendations were

then graded as weak or strong based on the majority opinion using the GRADE criteria.⁹

Recommendations

Recommendation 1: Sexual dysfunction and infertility frequently co-exist, as either cause or effect of the other, and hence evaluation of an infertile couple should include a detailed sexual history and physical examination. Grade of recommendation: Strong.

Infertility can exert a detrimental effect on the sexual, psychological, and marital life of a couple.¹⁰ Couples with infertility often shift their focus from “love-making” to “baby-making,” with a consequent impact on sexual intimacy and spontaneity. The reported prevalence of sexual dysfunction in infertile couples varies in different studies, possibly due to the wide range of research design and the heterogeneous literature.^{10,11} In a meta-analysis of studies of infertile couples, Starc et al.¹² reported a prevalence of female sexual dysfunction (FSD) ranging from 43% to 90%, and of MSD ranging from 48%-58%, while another review reported a prevalence of MSD ranging from 6.7% to 75%.²

The types of MSD encountered in infertile couples include erectile dysfunction (ED), premature ejaculation (PE), ejaculatory dysfunction, hypoactive sexual desire, impaired sexual satisfaction, and orgasmic dysfunction.² FSD in infertile

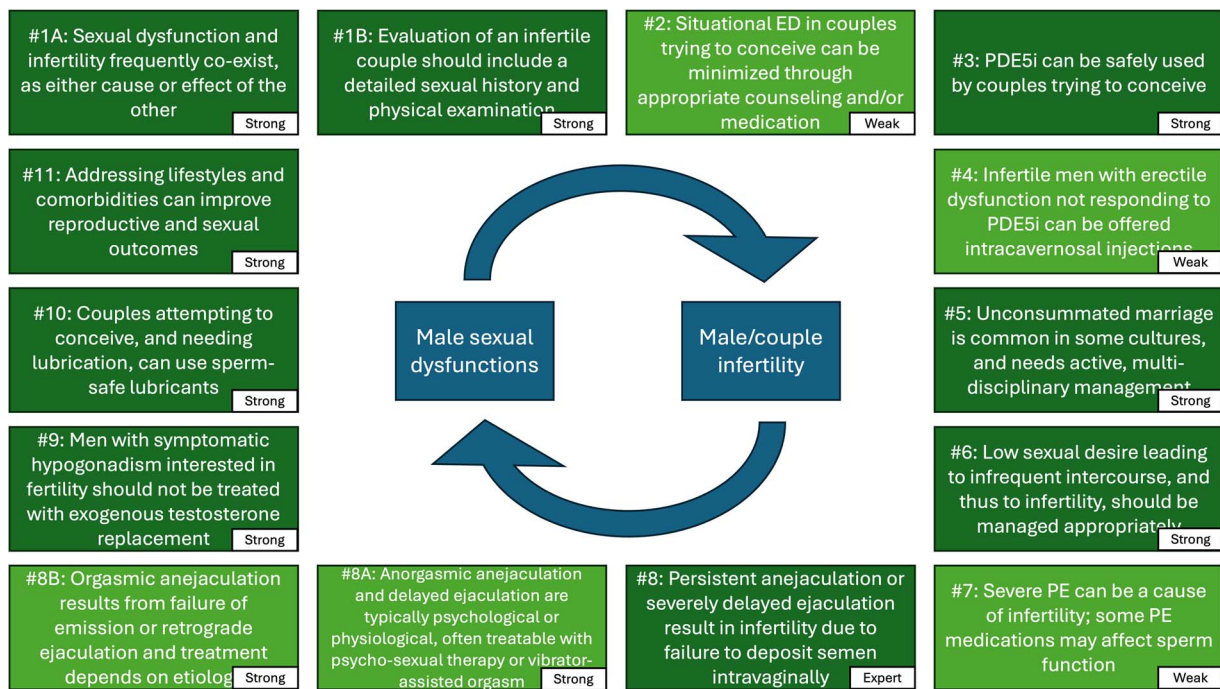


Figure 1. Recommendations for male sexual disorders associated with infertility.

couples includes hypoactive sexual desire, arousal dysfunction, anorgasmia, dyspareunia, and vaginismus, as well as anxiety, depression, and difficulties in marital relationships.¹¹

Couples undergoing assisted reproductive technology (ART) appear to be more vulnerable to sexual dysfunction.¹³ Expectations from partners, couples, and clinical teams regarding the success of ART procedures can lead to anxiety and distress. The need to provide one or more semen samples on demand via masturbation can precipitate ED or difficulty in ejaculation. Infertility is potentially humiliating and emasculating to men, and infertile men report higher rates of anxiety and depression than fertile men.¹⁴ The process of diagnosing and treating infertility can add significant stress to a couple's sexual relationship.¹⁰ Couples may increasingly see sexual intercourse as a duty, a way of procreation rather than recreation. This leads to decreased foreplay, reduced desire, diminished sexual arousal, and fewer signs of physical excitation. For men, this can promote the progression from subclinical to overt ED.¹⁵ Conversely, a reduction in coital frequency can be a contributing factor to infertility. This decrease is often a consequence of psychosocial or occupational stressors, with advanced age and erectile dysfunction also being identified as correlates of lower sexual frequency in subfertile couples.¹⁶ Therefore, a detailed history and physical examination should be obtained in all patients with MSD and infertility (Table 1).

Comprehensive clinical care within infertility services should include holistic care that addresses the sexual, psychological, and relational needs of individuals and couples facing infertility, and a sexual history should be an integral part of an infertility evaluation.^{14,17,18} Validated questionnaires aimed to assess sexual function of both partners may be used during clinical evaluation such as the International Index of Erectile Function (IIEF),¹⁹ the Premature Ejaculation Diagnostic Tool,²⁰ the Female Sexual Function Index,²¹ and the Orgasmometer.^{22,23}

Recommendation 2: Situational ED in couples trying to conceive can be minimized through appropriate counseling and/or medication. Grade of recommendation: Weak.

When couples are having trouble conceiving, or are undergoing treatment for fertility, they can experience significant stress that may result in ED. A recent meta-analysis comparing 2276 infertile men to 1492 fertile men demonstrated significantly higher likelihood of ED in infertile men (OR 2.92, 95% CI 1.71, 4.96), with the rates of ED ranging from 17.8% to 85.9%.¹⁰

A common cause of stress in couples facing infertility is having to time intercourse with ovulation. Many misconceptions exist regarding the correct frequency and timing of intercourse to optimize fertility. Previous work has studied live birth rates with different frequencies of intercourse.²⁴ Daily intercourse correlates with a higher live birth rate over alternate-day intercourse, which is superior to weekly intercourse. However, the benefit of daily intercourse over alternate-day intercourse is marginal.²⁴ Very specific recommendations regarding frequency of intercourse will likely induce unnecessary stress in infertile couples. Hence, couples should be counseled that frequent intercourse, at their convenience, during the fertile week is sufficient for optimizing the chances of pregnancy, and they should not stress about precise timing. On the other hand, couples should also be advised that they do not need to "limit" frequency of intercourse ("to conserve semen"), as more frequent intercourse is not associated with a lower chance of pregnancy.²⁵ Such an approach encourages a spontaneous, stress-free attitude toward intercourse when trying to conceive, and will help in avoiding performance pressure and resultant ED. If situational ED persists despite counseling and/or medication therapy, then further evaluation for ED with hormonal or glycolipid profile and possible penile dynamic duplex ultrasound is warranted.

Table 1. History and focused examination of infertile male.

Medical/sexual history	Infertility	Frequency of intercourse, duration of infertility, previous attempts at parenthood
	Relational status	Emotional status with wife/partner, partner age, female sexual dysfunction
	Sexual disorder	Erectile dysfunction, premature or DE, anejaculation (orgasmic/anorgasmic), low libido
	Validated questionnaires	IIEF, Premature Ejaculation Diagnostic Tool
	Comorbidities	Diabetes, hyperlipidemia, coronary artery disease, obesity, genitourinary infections, endocrine diseases
	Prior surgical history	Inguinal hernia, cryptorchidism, testicular torsion, hydrocelectomy, retroperitoneal and pelvic surgery
	Lifestyle factors	Smoking, alcohol, sleep disorders
	Medications	Beta-blockers, antidepressants, antipsychotics, chemo-radiotherapy
	Androgens	Intake of anabolic steroids, testosterone therapy, or bodybuilding supplements
	Physical Examination	Testis
Penis		Phimosis, frenulum breve, hypospadias
Breast		Gynecomastia
Other		Tall stature, eunuchoid body proportions, hair distribution

Recommendation 3: Oral phosphodiesterase 5 inhibitors can be safely used by couples attempting to conceive. Grade of recommendation: Strong.

Most cases of infertility-induced ED are not organic. Hence, the American Society for Reproductive Medicine Guidelines state that in patients with psychogenic ED, empirical psychotherapy, with or without a phosphodiesterase 5 (PDE5) inhibitor, under the supervision of an appropriate specialist with requisite expertise, should be offered.²⁶ These guidelines have been echoed elsewhere, with a sex therapist or counselor being considered an important part of a multidisciplinary team caring for couples with infertility.²⁷ For isolated peri-ovulatory ED, an oral PDE5 inhibitor may be offered as the first line of therapy. While any PDE5 inhibitor can be used on demand, some studies have suggested that daily tadalafil during the fertile period may be a better option, as it would eliminate the stress related to timing the medication with intercourse.^{27,28} In infertile men with ED, a detailed medical evaluation would be required if the cause of ED is unclear or other risk factors like obesity or metabolic syndrome are present.²⁹

The effect of oral PDE5 inhibitors on sperm has been extensively tested. Sildenafil and its metabolite UK-103320 have been detected in human semen, but at levels less than <0.0002% of the administered dose.³⁰ In vitro investigations of both sildenafil and tadalafil on ejaculated semen samples have demonstrated a dose-dependent increase in sperm motility, with potentially a bell-shaped effect.^{31,32} One study demonstrated a premature acrosome reaction.³³ PDE5 inhibitors have been demonstrated to exert a beneficial influence on the secretory function of the Leydig and Sertoli cells, the biochemical environment within the seminiferous tubule, the contractility of the testicular tunica albuginea, and the prostatic secretory function.³⁴

Clinical research has yielded conflicting results. While one study demonstrated some improvement in semen parameters in men taking PDE5 inhibitors,³⁵ a prospective, double-blind, randomized, crossover study evaluating the acute effects of both sildenafil (50 mg) and tadalafil (20 mg) in young, infertile men found a significant decrease in sperm rapid-progressive (class *a*) and total-progressive (classes *a* + *b*) motility after tadalafil [median value, 6.0% vs. 10.5% (Wilcoxon *z*-value, -2.76; *P* = .006), and 21.5% vs. 28.5% (Wilcoxon *z*-value,

-2.41; *P* = .015), respectively].³⁶ In contrast, a 2008 trial of 253 men randomized to tadalafil 20 mg daily vs placebo for 9 months demonstrated that tadalafil was noninferior to placebo in the proportion of subjects with 50% or greater reduction in sperm concentration.³⁷ Overall, multiple trials and meta-analyses have demonstrated improvements in sperm motility with the use of PDE5 inhibitor.³⁸⁻⁴⁰

It is important to consider that spermatogenesis takes 42 to 76 days.⁴¹ Since most men utilize PDE5 inhibitors on an “as-needed” basis, establishing a cause-and-effect relationship is difficult due to variability in dosage and frequency of use, compared to when semen samples are tested. Within the context of these limitations, the majority of evidence has not shown a detrimental effect of PDE5 inhibitors on semen parameters.³⁷⁻⁴⁰ No evidence suggests that oral PDE5 inhibitors affect fertilization or implantation, nor do they exhibit any teratogenicity when excreted in semen. Most importantly, no evidence demonstrates that PDE5 inhibitors limit fertility or live birth rate. Hence, oral PDE5 inhibitors can be safely used by couples attempting to conceive.

Recommendation 4: Infertile men with situational erectile dysfunction, who are non-responsive to oral phosphodiesterase 5 inhibitors, can be offered self-administered intra-cavernosal injection therapy. Grade of recommendation: Weak.

The need to perform intercourse on demand during the peri-ovulatory period can be very stressful⁴² and may result in situational ED. When the anxiety is very high, oral PDE5 inhibitors may not help these men. In such cases, intra-cavernosal injections (ICI) can provide an effective solution for the temporary situational ED.⁴³

Alprostadil, phentolamine, papaverine and other medication in various combinations and doses are highly effective in inducing erections.⁴⁴ No study has been done yet to assess the impact of ICI on sperm or pregnancy outcomes. However, intraurethral alprostadil and prazosin used to treat ED have not been shown to affect the motility, viability, or membrane integrity of human sperm⁴⁵; hence, we can infer that these ICI agents also will not affect sperm quality.

It should be noted that the safety of intraurethral agents has not been tested during human pregnancy or in couples trying to achieve pregnancy,⁴⁶ and female partners of men using intra-urethral prostaglandin should be aware of the

potential risk of vaginal absorption of prostaglandin during sexual activity, which can cause local side-effects such as irritation, burning, or discomfort. The newer topical agents to treat ED, such as Eroxon[®], require further studies on their safety in couples who are trying to conceive.⁴⁷ Meanwhile, ICI is an effective and safe method to enable anxious men with peri-ovulatory, situational ED to have penetrative intercourse when oral PDE5 inhibitors do not work or are contraindicated.

Recommendation 5: Infertility due to an unconsummated marriage is common in some societies and presents a complex problem that should be treated by a multidisciplinary team, addressing both male and female factors simultaneously, with a priority on fertility or sexual function as per the couple's goals. Grade of recommendation: Strong.

Unconsummated marriage (UCM) is defined as the inability of a heterosexual married couple to have penovaginal sexual intercourse.⁴⁸ UCM is largely underreported; hence, the real prevalence is unknown. In some Middle Eastern countries, UCM constitutes 4%-17% of the visits to sexual health clinics.^{49,50} UCM has been reported in orthodox Jews,⁵¹ traditional Muslim communities from Middle Eastern countries,⁴³ and in the South Asian region.⁵² The individual's educational status has no significant correlation with UCM, as studies have reported that most men in UCM were professionals or had university degrees.^{53,54}

Vaginismus (8.4%-81%) or ED (10.5%-61%) are the most common causes of UCM, followed by combined (male and female) factors (16.6%-26%), performance anxiety (4.1%-52.9%), and premature ejaculation (0.5%-52%).⁵⁵ Occasionally, the cause may be unrecognized homosexuality,⁵⁶ or physical conditions, such as phimosis, severe congenital penile curvature, buried penis, or childhood female genital mutilation, that may require surgical intervention.^{57,58} Couples may present as early as 1 day⁵⁹ and as late as 28 years⁵⁴ to seek treatment to consummate their marriage.

A detailed sexual history should assess the couple's level of sexual knowledge, degree of ED, presence of severe premature ejaculation, ignorance of sexual postures or techniques, learning disabilities/special needs, fear of sex, pain when attempting to penetrate, unrecognized alternative sexual orientation, past sexual abuse or trauma, sexual fears and phobias, unmet paraphilic needs for arousal, lack of lubrication during intercourse, porn addiction, as well as psychiatric and emotional issues. Examination of the penoscrotal region should be done to identify any physical cause. Even if there is a male factor, a gynecologist or a qualified medical professional should evaluate the female partner to rule out co-existing factors such as vaginismus.

Infertility is a direct consequence of UCM. Most couples present with the primary intent to consummate their marriage,⁴³ but sometimes their immediate concern is to conceive.⁶⁰ All efforts should be made to help the couple consummate the marriage, but if they prefer to focus on fertility first, then this should be respected after adequate counseling. This may happen if they have settled into a comfortable relationship where they are sexually fulfilled through other means of sexual engagement, or if they have come to terms with a sexless marriage that is otherwise emotionally and socially fulfilling.⁶¹ Sometimes, fertility is a priority because of their age or social pressures.

Treatment may fail if both partners are not treated together. A urologist working alone will usually attempt to restore erections but may fail to treat a concomitant female factor like vaginismus, which sometimes could be the cause of psychological ED. Similarly, a gynecologist may treat vaginismus but fail to provide adequate treatment for associated ED in a man whose high anxiety levels make him non-responsive to oral medications. Basic sex education should be provided to all patients, preferably using diagrams or pictorial images for better understanding. Patients should be encouraged to bring their partner/spouse, as this helps achieve better outcomes.

Sildenafil 50 mg on demand, over 1-3 months, resulted in a consummation rate of 84.6%-100%.⁶²⁻⁶⁴ Tadalafil in varying regimens (10 mg on alternate days, 10-20 mg on demand or 5 mg daily for a week) resulted in consummation rates of 67.7%-91%.^{53,65} ICI using papaverine and phentolamine helped 92.4% (221/239) of the couples to consummate.⁶⁶ An intensive, multidisciplinary approach involving a urologist, gynecologist, psychiatrist and sex therapist for a month helped 97% of 135 patients achieve penetrative intercourse.⁶⁷ Vaginismus can be treated by desensitization, graded vaginal dilator therapy, or other measures by a gynecologist or a qualified medical professional.⁶⁸ Childhood female genital mutilation might require deinfibulation surgery, while congenital penile curvature preventing consummation might need penile plication.^{57,58} An Iranian study reported a divorce rate of 24% (48/200) due to UCM.⁶⁹ Hence, UCM should be treated with urgency and addressed as soon as possible to prevent termination of the marriage/relationship.

When the couple is not interested in resolving the UCM and comes only for fertility, infertility treatment may be given priority. Sometimes, the couple may choose to treat UCM and infertility in parallel. If there is no problem with the semen quality and no female factor, then the couple can be instructed to perform intravaginal insemination at home.⁷⁰ If that fails, they may be referred to a gynecologist for intrauterine insemination (IUI) or in vitro fertilization (IVF).

Recommendation 6: Low male libido, resulting in infrequent intercourse, can be the primary cause of infertility and should be treated with a multidisciplinary approach, since the etiology can be varied. Strength of recommendation: Strong.

Infrequent intercourse is an important pointer towards impaired sexual desire but may also be the consequence of marital or personal stress. Loss of libido in the male could be a sign of male hypogonadism.⁷¹ While testosterone modulates erectile function at several levels,⁷² its main impact is on sexual desire.⁷³ Other endocrine factors affecting sexual desire include hyperprolactinemia and thyroid disorders (both hypo- and hyperthyroidism).^{74,75} Hyperprolactinemia can have a direct effect on and also cause a progressive decline in sexual desire and erections.⁷⁶⁻⁷⁸ Chronic distress can also potentially affect sexual as well as reproductive function, largely mediated by the hypothalamic-pituitary-gonadal (HPG) axis.⁷⁹

Psychological, social, and interpersonal issues may be important non-endocrine causes of low intercourse frequency. Low sexual desire can be a consequence of the intrusiveness of medical procedures in the setting of the infertile couple. Receiving a diagnosis of male factor infertility can shake a man's identity to the core, resulting in feelings of guilt, shame towards the partner, and lack of self-confidence, which can lead to isolation, anxiety, and depression.^{10,18,26,80} Intimacy

is often lost due to the request for timed intercourse or due to the man's perception of being involved only as a "sperm donor"⁸¹ for an ART procedure, which most males perceive as distressful and detrimental to their virility.² Additionally, in couples seeking a pregnancy, sex becomes progressively more focused on the reproductive aspects rather than on the pleasure aspects. Intercourse can thus become a significant source of distress and an "area of conflict".^{10,27}

Management of low sexual frequency in couples who are trying for a pregnancy should be provided by a multidisciplinary team including an andrologist, urologist, gynecologist, psychologist, sexologist, and endocrinologist as required.^{2,81} As detailed in Recommendation 9, testosterone replacement therapy should never be suggested to hypogonadal men who are looking for fatherhood, due to its suppressive effects on the HPG axis.⁸² A specialty evaluation by an endocrinologist should be considered for other endocrine disorders, and adequate treatments should be started as early as possible in order to prevent further impairment to sexual and reproductive health alike.

Most studies on this topic report that men shy away from psychological support, fearing to show weakness or lack of virility.²⁷ However, psychological support is necessary to prevent depression and the subsequent development of sexual dysfunction or their progression, from subclinical to overt.^{83,84} Psychological health is in a mutual relation with sexual function, as sexual activity can help patients cope with anxiety and depression⁸⁵; therefore, taking care of both is important to preserve the couple's well-being. Providing adequate psychological support to infertile couples can be beneficial in the long term, as some evidence suggests that partners coping successfully with their infertility grow more attached.^{11,86} Men are believed to show more affection following a diagnosis of male factor infertility, possibly in order to compensate for their guilt about their reproductive issues.¹⁸ Psychosexual support is sadly still lacking in many reproductive health clinics, despite its importance for infertile couples.⁸⁷

Recommendation 7: Premature ejaculation can be a cause of infertility if there is consistently ejaculation prior to penetration. However, medical therapy to treat this should be prescribed with caution as these medications may impair sperm quality. Grade of recommendation: Weak.

According to the "ejaculation distribution theory," men's duration of intercourse, assessed as intravaginal ejaculatory latency time (IELT), would fall within a continuum.⁸⁸ The majority would be close to the average IELT, with a median of 5.4 - 6 minutes,^{89,90} while a minority of men would nearly always be closer to early or delayed ejaculation (DE). At one extreme of this spectrum would be men who ejaculate before penetration (IELT = zero seconds).⁹¹

The prevalence of premature ejaculation (PE) ranges from 8%-31% in young men of reproductive age,^{92,93} but prevalence increases in men who are part of an infertile couple.^{14,29,94} This may be a result of the additional psychosocial factors that often lead to sexual dysfunction in infertile men. PE does not impact natural conception if discharge of sperm occurs after penetration. However, when discharge of sperm occurs before penetration, such as during foreplay, or with genital contact, then this may result in failure of natural conception, secondary to the inability of sperm to enter the vagina.²

Treatment of PE in the infertile couple includes the use of medications and behavioral or psychosexual therapy.^{2,95} Medications that have been used to treat PE include selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants, topical local anesthetics, tramadol, PDE5 inhibitors, and alpha-adrenergic blockers.⁹⁶ Commonly used SSRIs include paroxetine, sertraline, fluoxetine, and citalopram.⁹⁵ However, many of these SSRIs may have a negative impact on sperm parameters. Paroxetine has been shown to cause high DNA fragmentation in sperm, while sertraline has been shown to cause declines in semen concentration and normal morphology, and increased DNA fragmentation rates.^{97,98} Escitalopram has been reported to decrease sperm concentration, motility, and morphology.⁹⁹ While these effects appear to be reversible upon discontinuation of the medication, it is advisable to counsel couples about the potential for adverse fertility effects associated with SSRI use. Dapoxetine, a short-acting SSRI approved for on-demand treatment of PE in many countries, has shown 3.0-fold increases in IELT,¹⁰⁰ with early evidence suggesting no effect on sperm quality.¹⁰¹ There are only a small number of studies evaluating the impact of tricyclic antidepressants on sperm parameters, with conflicting results.^{102,103}

Topical anesthetic agents have been used to numb the glans and thus delay ejaculation, but they may affect the viability of sperm. One study showed a decrease in sperm viability from 70% to 0% after exposure to topical lidocaine spray, indicating a potential cytotoxic effect of the product on sperm.¹⁰⁴ Other studies show only a partial deleterious effect on semen quality, while others show none at low concentrations.¹⁰⁵⁻¹⁰⁸ Accordingly, couples trying for fertility may use topical agents to control PE but should be cautious and wipe off the anesthetic agent before penetration. Hence, it may be prudent to offer couples who are trying to conceive other forms of PE treatment based on psychosexual therapy.¹⁰⁹ When medication or therapy are ineffective in treating severe PE in an infertile couple, then at-home intravaginal self-insemination or IUI can assist in obtaining a pregnancy.⁷⁰

Recommendation 8: Persistent anejaculation (orgasmic or anorgasmic), characterized by the complete absence of an antegrade ejaculate, or severely delayed ejaculation leading to repeated failure to deposit semen intravaginally, will result in infertility. (Expert opinion).

Orgasm and ejaculation are two phenomena that usually occur simultaneously but are distinct and separate.⁸⁸ Rarely, a man can ejaculate without experiencing orgasm, a condition that has been termed anesthetic ejaculation.¹¹⁰ On the other hand, men can reach orgasm without the expulsion of semen; this has been referred to as aspermia¹¹¹ or orgasmic anejaculation. Some men are unable to reach orgasm despite adequate stimulation by coitus or masturbation and therefore do not ejaculate—this is termed anorgasmic anejaculation. Lastly, some men experience a marked and bothersome delay in reaching orgasm and ejaculation, leading to repeated failure to deposit semen intravaginally. The terms, "DE" or "Delayed Orgasmic Response" have been commonly employed to describe both delays in reaching orgasm, and failure to reach orgasm and ejaculation, but a more accurate distinction would be using "anorgasmic anejaculation" for the complete inability to reach orgasm and ejaculation, while reserving "DE" to when the man can reach an orgasm, at least sometimes, but requires prolonged

stimulation leading to a bothersome delay in reaching orgasm and ejaculation.

Recommendation 8A: Anorgasmic Anejaculation and Delayed Ejaculation are usually due to psychological or physiological causes but occasionally may have an organic etiology. In non-neurogenic cases, psycho-sexual therapy or vibrator-assisted orgasm may resolve the problem and allow natural conception. Otherwise, assisted reproduction using sperm obtained by masturbation, vibratory stimulation, electro-ejaculation or surgical retrieval would be required. Grade of recommendation: Strong.

DE has a relatively low prevalence, estimated at around 1.5/1000 men in the general population, and is a largely under-investigated and under-reported sexual dysfunction.^{112,113} It can be a significant source of distress in couples, increasing anxiety and depression scores as well as decreasing intercourse satisfaction.¹¹² In more severe forms of DE, it is not uncommon for men to give up on sexual intercourse without ever reaching orgasm (anorgasmic anejaculation).¹¹⁴ In the majority of cases, no organic cause is found and the problem is attributed to a high physiological threshold for reaching orgasm,¹¹⁵⁻¹¹⁷ or to psycho-sexual inhibitions resulting from intra-psychic or relational factors,^{116,118-121} or lack of interest toward the partner.^{116,118} Other causes include idiosyncratic masturbation styles, pregnancy fears, overly strict religious upbringing, performance anxiety,¹¹⁶ traumatic sexual experiences,¹²² inadequate sexual techniques, unmet needs for specific types of sexual arousal, or overcontrolled personality traits.¹¹⁸

Organic causes that need to be ruled out include neurological damage which is commonly due to multiple sclerosis¹²³ or diabetic neuropathy,^{123,124} endocrine diseases (eg, hypogonadism),¹¹⁹ hyperprolactinemia,¹²⁵ hypothyroidism,^{119,126} and the concomitant use of psychotropic medications such as SSRIs.¹²⁷

Men with spinal cord injury (SCI) constitute a separate group of men with a neurologically obvious cause for failure to reach orgasm and ejaculation and may be treated by vibrator stimulation or electro-ejaculation (EEJ)¹²⁸ depending on the level of lesion or may need surgical sperm retrieval and assisted reproduction.

Delayed ejaculation/anorgasmic anejaculation can be global (total), with difficulty to reach orgasm in all situations, whether by masturbation or intercourse, or it may be situational, with difficulty to reach orgasm in some situations, or on some occasions. Perioviulatory anejaculation is a form of situational anejaculation that can hamper fertility. In this condition, the pressure to have intercourse on specified days and times, based on fertility probability, leads to performance anxiety with resultant ED and/or inability to ejaculate.

Treatment will depend on the cause. If there is an organic problem, then that should be addressed first. If no relevant comorbidity is found, then several strategies are available for the treatment of DE/anorgasmic anejaculation of psychogenic/physiological origin. Sex therapy would be the treatment of choice,^{119,122,129} considering that these conditions pose a significant psychological burden on the couple and can be a source of distress; however, while potentially useful, results of sex therapy are not always reliable, and the couple need to establish a good relationship with the sex therapist.^{118,129} There is a lack of validated outcome measures

(Althof 2012), and when a couple's focus is infertility, the couple often lacks the patience required for successful sex therapy.

Medical therapy does not appear to be effective. Bupropion¹¹² and cabergoline¹³⁰ have been investigated as possible treatments, but their efficacy is uncertain, and these medications are not approved for clinical use for DE.¹³¹ Other medications, such as amantadine, cyproheptadine, oxytocin, buspirone, midodrine, and yohimbine, also lack enough supporting evidence to be recommended for clinical practice¹³² and therefore, should be considered only on an individual trial basis. Medications with alpha-agonist activity, such as imipramine & ephedrine, have also been proposed but have a low success rate in these cases.¹³³

Prolonged stimulation with penile vibrator stimulation (PVS) can result in orgasm and ejaculation in a significant proportion of men with non-organic DE or anorgasmic anejaculation.^{134,135} In those who succeed with PVS, its regular use may lead to restoration of the ability to reach orgasm during intercourse, and natural pregnancy. Those who succeed in ejaculating with PVS or masturbation, but not during intercourse, can be instructed to perform intra-vaginal insemination at home if the semen quality is good, or can proceed to IUI. In those in whom PVS fails, electro-ejaculation usually succeeds in producing an ejaculate since there is usually no organic problem.

If irreversible neurological damage is present, it can permanently result in DE/anorgasmic anejaculation. In such cases, PVS may be able to induce ejaculation in order to retrieve a semen sample to be used for IUI or intra-vaginal insemination at home.^{123,136,137} If this fails, then EEJ could produce a sample that could be used for IUI or intracytoplasmic sperm injection (ICSI).¹²³ Finally, surgical sperm retrieval can be performed in conjunction with ICSI.¹³⁸

Recommendation 8B: Orgasmic anejaculation (reaching orgasm without ejaculation) is due to an organic cause (anatomic obstruction of ejaculatory and prostatic ducts, neurogenic damage, medication, or severe hypogonadism); it may be treated by medical therapy, penile vibratory stimulation, electro-ejaculation, or sperm retrieval and assisted reproductive technology. Grade of recommendation: Strong.

In the case of orgasmic anejaculation, the individual reaches a climax, experiences orgasm, but does not ejaculate, either due to failure of emission (Phase 1 disorder), retrograde flow of semen into the bladder (Phase 2 disorder), or failure of antegrade propulsion of semen (Phase 3 disorder). The various etiologies are summarized in Table 2.¹³⁹ If only the ejaculatory ducts are affected either due to its absence as a consequence of vas aplasia or obstruction due to a large prostatic cyst, then there will be low volume ejaculate present which is a distinct and separate condition from orgasmic anejaculation.^{140,141} While the majority of men with severe hypogonadism has preservation of their antegrade ejaculation (AE), in select cases of severe hypogonadism due to sudden bilateral loss of testis (related to torsion or trauma), the authors have clinically seen this subset of men experience complete loss of ejaculation and therefore should be considered a possibility as an underlying etiology.

The diagnosis is based on history and urine examination. Patients may report cloudy urine following orgasm and a

Table 2. Causes of orgasmic anejaculation.

	Phase 1 Disorder Failure of Emission	Phase 2 Disorder Failure of Bladder Neck Closure (Retrograde Ejaculation)	Phase 3 Disorder Failure of Antegrade Propulsion
Anatomical causes	Infective obstruction of ejaculatory & prostatic ducts (eg, GU tuberculosis)	Trauma to bladder neck; Bladder neck incision; Transurethral resection	Urethral obstruction (pouch, diverticulum, stricture); Surgical disruption of bulbocavernosus muscle
Neurogenic causes	Diabetic neuropathy; α -blockers; Spinal cord injury; Multiple sclerosis; Retroperitoneal surgeries (RPLND, Abdominal aortic, rectal prolapse, radical cystectomy); Spine surgery; Lumbar sympathectomy	Diabetic neuropathy; α -blockers; Spinal cord injury; Multiple sclerosis; Retroperitoneal surgeries (RPLND, Abdominal aortic, rectal prolapse, radical cystectomy); Spine surgery; Lumbar sympathectomy	Pudendal nerve neuropathy or damage; Myopathy affecting bulbocavernosus muscle
Endocrine causes	Severe hypogonadism – primary or secondary		
Other causes		Congenitally wide bladder neck; Idiopathic	

Abbreviations: RPLND, retroperitoneal lymph node dissection.

diagnosis of retrograde ejaculation (RE) is confirmed if a post-orgasm urinalysis reveals sperm.¹²⁴ For men who desire paternity, treatment of neurogenic orgasmic anejaculation may be possible, in some cases, with medical therapy to achieve AE. If this fails, or is not feasible, then sperm retrieval techniques for use for assisted reproduction are indicated.^{124,137} Medications for the treatment of neurogenic orgasmic anejaculation include sympathomimetics, alpha-agonists, anticholinergics, antihistamines, and tricyclic antidepressants^{124,137} (Table 3).

In a double-blind controlled study looking at 4 different alpha-adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine, and pseudoephedrine), with or without antihistamines, for treatment of anejaculation in one patient who underwent an retroperitoneal lymph node dissection (RPLND), the authors found that all four medications produced an antegrade ejaculate, and that 4 days of treatment was more effective and better for sperm motility than a single dose.¹⁴² In a controlled study of 23 men with RE secondary to diabetes, treatment with imipramine, pseudoephedrine, or a combination of both was evaluated. When both medications were administered together, 61% of the participants¹⁴² were able to ejaculate suggesting that the combination therapy was more effective than either medication alone.¹⁴³ When RE has been confirmed by post-ejaculate urinalysis, sperm can be retrieved from the urine and used for IUI or IVF depending on the sperm count and motility. Alkalinizing the urine with agents like potassium citrate or sodium bicarbonate taken orally for 2 to 3 days prior, will make the urine more sperm-friendly and improve motility of the recovered sperm. Once the urine is alkalinized, the man masturbates to orgasm and then immediately voids the urine which is centrifuged to separate the sperm. If the motility is still poor, then an alternative method is to empty the bladder and then instill sperm-washing media into the bladder using a urethral catheter. The patient then masturbates to orgasm and immediately voids the media, which is centrifuged to recover sperm.¹²⁴

Recommendation 9: Men with symptomatic hypogonadism who are interested in fertility should not be treated with exogenous testosterone replacement and instead may be

treated with selective estrogen-receptor modulators, aromatase inhibitors, or gonadotropins, which will increase testosterone while maintaining fertility. Strength of recommendation: Strong.

Hypogonadism is diagnosed when there are symptoms attributable to testicular hypofunction associated with low serum testosterone levels. Total testosterone should be tested twice in the early morning on separate days before considering treatment for low testosterone. The American Urological Association guidelines consider a value <300 ng/dl significant,¹⁴⁴ while the European Society of Endocrinology has suggested a cut-off value of 350 ng/dl.¹⁴⁵

When low testosterone is diagnosed in infertile men with sexual dysfunction or symptoms of hypogonadism, a clinical examination and hormone profile should be performed to differentiate between primary and secondary causes of low testosterone. This will help guide the therapy for those men with symptomatic low testosterone and who desire fertility.

Exogenous testosterone is a potential contraceptive and should not be used by men with low testosterone who are trying for conception.¹⁴⁶ Exogenous testosterone will suppress the secretion of follicle-stimulating hormone and luteinizing hormone, thus suppressing spermatogenesis.¹⁴⁷ The use of exogenous testosterone resulted in azoospermia in 77% of men with prior documented fertility in a median time of 100 days, and only 34% recovered their baseline sperm concentration after discontinuation of exogenous testosterone.¹⁴⁸ Medications that can be used to raise testosterone levels without compromising fertility are listed in Table 4.

Selective estrogen-receptor modulators, such as clomiphene and tamoxifen, are commonly used but are an off-label indication in male infertility.^{149,150} Aromatase inhibitors (anastrozole and letrozole) are prescribed when there is a low testosterone-to-estradiol ratio (< 10:1). They are also an off-label indication, with low libido (6.2%) as the most commonly reported sexual side effect.¹⁵¹ This should be monitored during follow-up and estradiol levels should not be allowed to go too low. In adolescents with Klinefelter's syndrome or young men who become hypogonadal after completing systemic

Table 3. Medication used in the treatment of RE. Note that the use is considered “off-label.”

Drug	Dosage	Time	Side effects
Ephedrine	15-100 mg PO daily (120 mg BID)	60-120 min before effect after 2-4 weeks	hypervigilance, anxiety, hypertension, palpitations, tachycardia, headache, dizziness and insomnia
Synephrine Pseudoephedrine	60 mg IV 60-120 mg PO daily (240 mg PO daily)	60 min 120-150 min before	hypervigilance, anxiety, hypertension, palpitations, tachycardia, headache, dizziness and insomnia
Imipramine	25-75 mg PO daily (50 mg PO daily)	Effect after 1 week	dry mouth, constipation, red vision, urinary retention, sometimes confusion or memory issues, orthostatic hypotension, dizziness, sedation, reduced libido, erectile dysfunction and difficulty achieving orgasm
Imipramine + Pseudoephedrine	50-120 mg PO daily	60 min before effect after 2 weeks	See above ? more pronounced
Midodrine	4-40 mg IV 15 mg PO daily	30-120 minutes	
Phenylpropylamine Brompheniramine	150 mg PO daily 14-24 mg PO daily 16 mg PO daily	120 minutes 12 hours before after 2 week induction	dizziness, dry mouth, constipation, urinary retention, blurred vision, tachycardia
Brompheniramine & phenylephrine	112 mg PO daily	N/A	
Chlorpheniramine & phenylpropylamine	50 mg PO daily	N/A	
Dextroamphetamine	20 mg PO daily		
Amoxapine	50 mg PO daily	Effect after 1 month	Unclear, probably similar to imipramine

Adapted from Kamischke and Nieschlag, 2002.¹³²

Table 4. Commonly used fertility-preserving medications to treat symptomatic hypogonadism.

Medication	Route	Dosage and frequency	Side effects
Clomiphene (<i>off-label</i>)	Oral	25-50 mg every 1-2 days	Gynecomastia, nipple tenderness, blurred vision, dizziness, leg swelling, hot flashes, bloating
Tamoxifen (<i>off-label</i>)	Oral	20 mg daily	Hot flashes, night sweats, nausea, headaches, fluid retention, liver damage, blood clots
Anastrozole (<i>off-label</i>)	Oral	0.5-1 mg every 1-3 days	Hot flashes, headache, nausea, high blood pressure, rash, reduced libido
Letrozole (<i>off-label</i>)	Oral	2.5 mg every 1-3 days	Hot flashes, difficulty sleeping, fatigue, high cholesterol, nausea
Human chorionic gonadotropin	Subcutaneous/ intramuscular	1500-5000 IU 2-3 times per week	Gynecomastia, headache, fatigue, mood changes, high blood pressure, fluid retention
Human menopausal gonadotropin (with human chorionic gonadotropin)	Subcutaneous/ intramuscular	75 IU 2-3 times per week	Gynecomastia, mood changes, depression, irritability, headache, fatigue

therapy for malignancy, the simultaneous administration of exogenous testosterone combined with injectable low-dose human chorionic gonadotropin (hCG) (500 IU) every two days may be an option to preserve fertility.¹⁵² However, further studies are needed to validate the use of exogenous testosterone therapy in combination with low dose hCG or with an aromatase inhibitor for fertility preservation.¹⁵³ In select cases, hCG monotherapy may also be an option to treat some hypogonadal men.¹⁵⁴

Recommendation 10: Couples attempting to conceive may use lubrication, if needed, and should be advised to use sperm-safe lubricants. Grade of recommendation: Strong.

Use of vaginal lubricant (VL) during intercourse by couples trying to conceive is common. In the United Kingdom, approximately 10% of couples trying to conceive reported use of VL.¹⁵⁵ Among 296 U.S. couples trying to conceive, 28.6%

used lubricants occasionally, while 14.3% reported frequent use.¹⁵⁶ A legitimate concern is whether these lubricants could affect sperm function and reduce the chances of natural conception. A wide range of natural and formulated lubricants are available. These include natural oils (olive oil, sesame oil, canola oil, coconut oil), saliva, egg-white, baby oil, petroleum-based lubricants (petroleum jelly or mineral oil), silicone lubricants, water-based products containing glycerin, water-based lubricants free of glycerin, and hydroxyl-ethylcellulose-based lubricants specially formulated to mimic the pH and osmolality of semen.

A large number of in vitro studies have been performed comparing the effect of these various lubricants on sperm motility; some studies have also assessed viability and sperm DNA fragmentation.¹⁵⁷ A comprehensive description of these studies and their outcomes can be found in a review by Mesen and Steiner¹⁵⁸ and in a recent systematic review by

Gumerova et al.¹⁵⁹ The latter review rated all lubricants using the RAG (red, amber, green) categorization. Four lubricants (Pre-Seed™, Johnson's® Baby Oil, egg white, canola oil) were rated green (no detrimental effect on sperm), six lubricants (K-Y® Jelly, Astroglide®, Replens™, olive oil, Yes®, K-Y® Jelly Warming) were rated red (negative effects on sperm), and another twenty-five were rated amber (inconclusive). The amber group included Conceive Plus®, which, like Pre-Seed™, is a hydroxyethylcellulose-based lubricant and has similar properties to Pre-Seed™ in terms of maintaining sperm vitality and motility.¹⁵⁷

Despite the potential negative effects of VL on sperm motility, they do not seem to negatively impact natural fertility. A prospective cohort study involving 6467 women, pooled from two ongoing prospective preconception cohort studies in Denmark and North America, found that lubricant use was not associated with a decrease in fecundity.¹⁶⁰ Similar findings were reported from a 2012 prospective cohort study of 296 women trying to conceive. In this study, the most commonly used lubricants were K-Y Jelly® (44%) and Astroglide® (20%), which are water-based, glycerol-containing lubricants considered harmful to sperm, with only 9% of women using Pre-Seed™, which is considered sperm safe.¹⁵⁶ From this study, Steiner et al.¹⁵⁶ postulated that even though lubricants may be sperm toxic, sperm deposited in the upper vagina during intercourse rapidly move into the cervix,¹⁶¹ likely minimizing any exposure to lubricants remaining on the external genitalia and lower vagina.

Since multiple in vitro studies have shown that sperm-safe lubricants do not impair sperm motility or viability, and clinical data suggest they may not hamper natural fertility, couples trying to conceive need not suffer dyspareunia due to vaginal dryness and may use a sperm-safe lubricant as per preference, availability, and cost.

Recommendation 11: Optimization of comorbid conditions/illness and appropriate lifestyle changes may improve both sexual and reproductive health. Grade of recommendation: Strong.

While the immediate goal of a couple's fertility evaluation and treatment is to achieve a healthy pregnancy, the ultimate desired outcome is having a healthy child. Both ED and fertility have been suggested to be markers of overall health. As such, optimizing comorbid conditions may not only improve sexual and reproductive health but may also benefit the offspring.¹⁶²⁻¹⁶⁴

Smoking

Smoking is one of the most important modifiable risk factors for ED and fertility. A large meta-analysis of over 5000 men has demonstrated that sperm counts and motility are lower in men who smoke.¹⁶⁵ Other forms of tobacco and nicotine may also have an adverse effect on sperm.¹⁶⁶ Sperm concentration, motility, morphology, and percentage viability were all lower in severe (>6 times a day) chewing tobacco users vs mild (< 3 times a day) users.¹⁶⁷ Similarly, sperm concentration and counts were lower among daily e-cigarette users.¹⁶⁸ Quitting smoking can lead to improvements in sperm concentration and semen volume, which has been observed at three months after quitting.¹⁶⁹

Smoking is also a risk factor for ED, mediated through endothelial damage and dysfunction.¹⁷⁰ The odds ratio of

smokers having ED ranges from 1.4 to 3.1.¹⁷¹ Smoking is even more of a risk factor for ED in young men less than 40 years old, making it a more important risk factor for those trying to conceive, since they are likely to be in this age range. E-cigarettes, a new trend in recent years, may also have a detrimental effect on erections.¹⁶⁶ However, the evidence for this is less robust. Quitting smoking can lead to an improvement in blood flow in the penis, which can be seen as early as 24 hours after stopping the exposure.^{170,172} Improvements in erectile function after quitting smoking have been reported for up to 1 year, though it is unlikely that erections will return completely to baseline. Of note, younger men are more likely to note improved erections after quitting smoking.¹⁷¹ All tobacco and nicotine use should be discouraged in men trying to conceive to improve outcomes for pregnancy, erections, and the child's health.^{171,173}

Obesity, metabolic syndrome, and diabetes

Obesity can lead to subfertility and ED through multiple mechanisms.¹⁷⁴ Obesity affects the HPG axis through a decrease in testosterone and increase in estrogen. Obesity has been associated with worsening semen parameters in multiple meta-analyses.^{175,176} Interestingly, one large study demonstrated that both underweight and overweight men had decreased semen parameters.¹⁷⁷ Beyond semen parameters, obesity is correlated with worsening outcomes for both natural pregnancy and ART procedures.¹⁷⁴ Other conditions associated with obesity, namely metabolic syndrome and diabetes, have both been linked with ED and subfertility.

While the above associations are informative for patients, the most important consideration is whether improving these health conditions can enhance both the patient's erections and semen parameters. Comparing men who exercise regularly to those who are sedentary reveals that men who exercise have better semen parameters.¹⁷⁸ Though regular exercise may generally improve semen parameters, current research does not delineate the optimal type and duration of exercise for this purpose.

A model of dramatic improvement of obesity and metabolic syndrome is gastric bypass surgery. Though testosterone levels increase after gastric bypass surgery, the effect on semen parameters is still not clear, with literature showing mixed results.^{174,179-181} Small studies have revealed improvement in erections after bariatric surgery.¹⁸² Men attempting to conceive, and who are experiencing ED, should at least be encouraged to optimize metabolic health with diet and exercise.

Medications for obesity and diabetes may also affect semen parameters. Some have suggested that metformin may affect semen parameters, but it is unclear whether these parameters improve or worsen.^{183,184} Newer glucagon-like peptide-1 (GLP-1) receptor agonists are becoming more prevalent in use and may impact erectile function.¹⁸⁵ A retrospective cohort study of men with type 2 diabetes compared changes in IIEF-5 scores over 1 year between men on metformin alone vs metformin and a GLP-1 receptor agonist.¹⁸⁶ The authors found significant increases in both free and total testosterone levels, and an increase in IIEF-5 scores of about 2 points in the combination group when compared to the metformin group alone. On a multivariate analysis, addition of GLP-1 receptor agonists was independently associated with improvement in IIEF. In a study on rats

with induced type 1 diabetes, liraglutide for 4 weeks resulted in improved erectile function with increased intracavernous pressure/mean arterial pressure.¹⁸⁷ Zamponi et al.¹⁸⁸ found that patients treated with “newer” antihyperglycemic medications, including Dipeptidyl-peptidase-4 inhibitors (DPP4-i), sodium-glucose cotransporter-2 inhibitors (SGLT2-I), and GLP-1 receptor agonists, were less likely to have an absence of response to PDE5 inhibitors. Bajaj et al.¹⁸⁹ performed an exploratory analysis of data from the REWIND trial comparing diabetic men taking dulaglutide vs diabetic men taking placebo; they found a lesser reduction in the EF score of IIEF in the dulaglutide group compared to placebo as well as a lesser decline in overall satisfaction score.

While any drug class utilized to optimize overall health may improve ED in the setting of infertility, ensuring safety for fertility is imperative. To that end, some have suggested that GLP-1 receptor agonists may be beneficial for male infertility as well.¹⁹⁰ GLP-1 receptors have been found in sperm cells and Sertoli cells. Animal studies demonstrate improved sperm motility after administration of GLP-1 receptor agonists.¹⁹¹ A small, randomized, double blind placebo-controlled trial demonstrated no change in semen parameters, luteinizing hormone, follicle stimulating hormone, or total testosterone after four weeks of treatment with dulaglutide vs placebo, though this is a very short duration.¹⁹² Another RCT demonstrated that men who lost weight with liraglutide maintained improved semen parameters for 1 year.¹⁹³ With the current data at hand, no detrimental effects, and possibly benefit, of GLP-1 receptor agonists on spermatogenesis and male fertility have been identified.

Conclusion

Male sexual dysfunction may often be present in couples with infertility. It may predate and contribute to infertility, or it may arise as a consequence of infertility. Clinicians handling infertility should be well-versed in the management of sexual dysfunctions. The initial patient encounter offers a valuable opportunity to identify these issues by asking targeted questions about erection, penetration, intra-vaginal ejaculation, frequency of intercourse, use of lubricants and lifestyle risk factors. Such inquiries will help identify any problems that need further questioning and evaluation, and lead to appropriate counseling and tailored treatments aimed at maximizing fertility potential and restoring a satisfactory sexual life. The recommendations provided in this review are based on a comprehensive examination of the current literature, offering clinicians the most up-to-date evidence on managing sexual dysfunction in men with infertility.

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