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Published in:
Sexual Medicine

DOI:
10.1016/j.esxm.2021.100377

Publication date:
2021

Document version:
Final published version

Male Sexual Dysfunctions in the Infertile Couple—Recommendations From the European Society of Sexual Medicine (ESSM)

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ABSTRACT

Introduction: Sexual dysfunctions (SDs) have been frequently reported among male partners of infertile couples due to psychogenic, relational and/or organic issues related with the inability to conceive. Likewise, male infertility (MI) could be a consequence of sexual dysfunctions.

Aim: To review the evidence on the prevalence and treatment of male SDs in men of infertile couples and provide clinical recommendations on behalf of the European Society of Sexual Medicine (ESSM).

Methods: The MEDLINE database was searched in September 2019 for randomized clinical trials (RCTs), meta-analyses and open-label prospective or retrospective studies investigating the presence of erectile dysfunction (ED) and/or ejaculatory dysfunctions (EjDs) and/or low sexual desire (LSD) in conjunction with infertility.

Main Outcome Measure: The panel provided statements on: (i) Prevalence and association between SDs and MI; (ii) Treatment of male SDs in men of infertile couples.

Results: ED has been reported in 9% to 62% of male partners of infertile couples, with severe impairment observed in only 1% to 3% of ED cases. Moreover, worse semen parameters have been associated with greater ED severity. Phosphodiesterase type 5 inhibitors (PDE5is) can be safely used to treat ED among patients seeking fatherhood. Male partners of infertile couples are at higher risk of premature ejaculation (PE). Retrograde ejaculation (RE) and anejaculation are a cause of MI and can be managed with electroejaculation (EEJ) or penile vibratory stimulation (PVS) or, alternatively, with oral treatments, however the latter with limited documented success. Low sexual desire has been reported by one third of men of infertile couples.

Conclusion: ED could significantly affect male partners of infertile couple; PDE5is should be suggested to ensure an effective and satisfactory sexual relationship of the couple. Anejaculation and RE should be considered as a possible cause of MI and treated accordingly. Low sexual desire is frequently reported among men of infertile couple and could be a symptom of other systemic conditions or psychological distress. **Capogrosso P, Jensen CFS, Rastrelli G, et al. Male Sexual Dysfunctions in the Infertile Couple—Recommendations From the European Society of Sexual Medicine (ESSM). Sex Med 2021;9:100377.**

Key Words: Sexual Dysfunctions; Infertility; Erectile Dysfunction; Ejaculation Disorders; Low Sexual Desire

Received November 18, 2020. Accepted April 3, 2021.

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https://doi.org/10.1016/j.esxm.2021.100377

INTRODUCTION

Couple infertility is defined as the inability to conceive after 12 months of regular sexual intercourse.[1] Population based studies have reported that about 15% of couples may suffer from infertility, thus representing a considerable issue for the global health community.[2–4] In this context, approximately 40% to 50% of infertile couples are unable to conceive as a consequence of male reproductive impairment.[2–4]

Sexual dysfunctions (SDs) affect a large proportion of men with a detrimental impact upon subjective quality of life (QoL)[5,6] Epidemiological data suggest that about 50% of the male population report at least one SD during their lifetime.[7] Dysfunctions may involve several aspects of sexuality, including sexual desire, erectile function (EF), ejaculation and orgasm.

Recently, a comprehensive review reported several studies evaluating the association between male infertility (MI) and SDs.[8] The link between these conditions is essentially bi-directional: on one hand patients suffering from fertility issues are commonly struggling with feelings of depression and anxiety, which could affect both the male and female partner, with a detrimental impact on sexuality.[8] Specifically, psychogenic erectile dysfunction (ED) and low sexual desire (LSD) may be the consequence of a stressful sexual context engendered by the inability to conceive.[9] Likewise premature ejaculation (PE) could be the consequence of increased anxiety in the male partner.[5,9] On the other hand, some severe SDs could significantly affect male reproductive function and have been recognized as the cause of MI in a range between 0.4% and 4.6% of cases.[8] Ejaculatory dysfunctions (EjDs), thus including retrograde ejaculation (RE) and anejaculation, for instance, have been shown to represent the main cause of MI in 1.2% and 2.2% of cases.[10] At the same time severe ED could impair fertility by reducing the frequency of vaginal intercourses.[11]

Given the mutual association between MI and SDs, we aimed to review the evidence on SDs and MI and to provide official position statements regarding the prevalence and management of SDs among patients with MI on behalf of the European Society of Sexual Medicine (ESSM).

EVIDENCE ACQUISITION

Literature Search and Study Eligibility

We searched MEDLINE using the terms: ("erectile dysfunction" OR "impotence" AND "infertility" OR "infertile" OR "subfertile" OR "azoospermia") for ED; ("ejaculation" AND "premature" OR "retrograde" OR "anejaculation" AND "infertility" OR "infertile" OR "subfertile" OR "azoospermia") for EjDs; ("desire" OR "libido" AND "hypoactive" OR "low" AND "male" OR "men" AND "infertility" OR "infertile" OR "subfertile" OR "azoospermia") for LSD. Randomized clinical trials (RCTs), meta-analyses and open-label prospective or retrospective studies investigating the prevalence and treatment of ED, EJDs and LSD among patients suffering from couple infertility (up to September 2019) were included. The research diagram is reported in Figure 1.

Data Extraction

Studies were categorized according to the specific fields of investigation (e.g. ED, EJDs or LSDs). Data regarding study design, population baseline characteristics, prevalence of SDs, and modality of SDs assessment were collected. Moreover, the estimates of the association between SDs and MI or semen parameters were recorded. For studies reporting management of male SDs among infertile couples, data on treatment protocols and improvement of specific outcomes related to each SDs were considered.

Review Methods

Abstracts were reviewed by three different subgroups of the panel for relevance to the defined review question (ED: *PC, JT, GIR*; EjD: *CFS; AF*; LSD: *GR, AR*). If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. Moreover, other studies relevant to the research question were retrieved from the reference lists of selected papers. Included studies were analysed and summarized after an interactive peer-review process of the panel. Clinical statements were provided for: (i) Prevalence and association between SDs and MI; (ii) Treatment of male SDs in patients suffering from couple infertility. The statements were internally discussed and the level of evidence (LoE) was provided according to the Oxford 2011 Levels of Evidence criteria; moreover, the quality of evidence was graded by applying the Oxford Centre for Evidence-Based Medicine recommendations (https://www.cebm.net/2011/06/2011-oxford-cebm-levels-evidence-introductory-document/);. No recommendations were given when the available data were insufficient to draw conclusions. Disagreements were resolved by consensus.

No ethical committee approval was needed due to the specific design of this research.

ERECTILE DYSFUNCTION

Statements

1 Prevalence and association
- Male partners of infertile couples are at higher risk of reporting ED (Level 3; Grade C)
- Worse seminal profile is associated with more severe ED (Level 3; grade C)

2 Treatment
- Phosphodiesterase type 5 inhibitors (PDE5is) can be safely administered to infertile men suffering from ED (Level 1; grade B)
- Further studies are needed to investigate the possible effect of PDE5is in terms of sperm parameters

Evidence

1. Prevalence and association

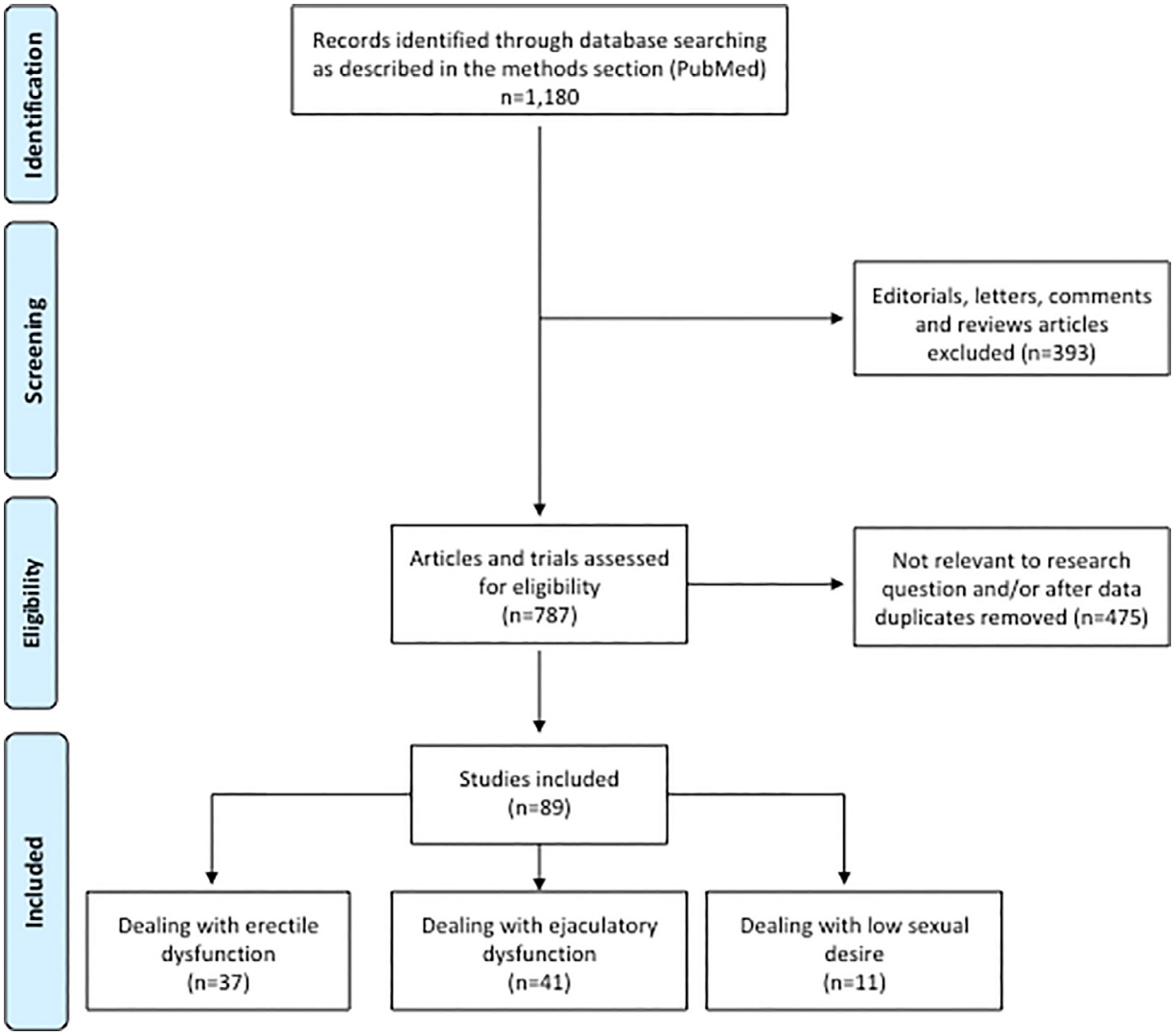

Figure 1. Flow charts showing inclusion and exclusions criteria of articles for the review.

The first report on ED and infertility was published by Berger et al in 1980.[12] They reported at least temporary ED in 10 out of 16 azoospermic men. In 1986 Chelo et al[13] interviewed 61 men of infertile couples finding that 42% of them thought that "people" consider the lack of children as related to male impotence. After these preliminary studies, we identified, 8 case-control studies[14–21] and 14 cross-sectional single arm studies[5,22–34] investigating the association between ED and infertility (Table 1). Furthermore, the association has been addressed in a RCT by Coward et al.,[35] investigating ovarian stimulation before intrauterine insemination. The vast majority of these studies applied the validated International Index of Erectile Function (IIEF) questionnaire to investigate ED, reporting a prevalence of EF impairment ranging from 9% to 62%, being mild to moderate in most of the cases with severe ED in only 1% to 3% of patients (Table 1).

In a secondary analysis of the RCT by Coward et al.,[35] the authors looked at ED in men of couples with unexplained infertility. Out of 708 men, ED was found in 9% of cases as assessed with the IIEF. They reported that lower fertility related quality of life was associated with higher risk of ED (OR:1.3; 95%CI: 1.16 - 1.46). It should be noticed that ED assessment was not the primary outcome of this trial. In a case-control study, Gao et al.[19] compared 1468 infertile men and 942 fertile controls, reporting a higher prevalence of ED (IIEF-5 score < 22) in the infertile group (18.05% vs 8.28%, $P < .001$). Similarly, Lotti et al[17] compared 448 men of infertile couples and 74 age-matched fertile men. They reported higher prevalence of ED (IIEF-EF score < 26) in infertile males compared with controls (18.3 vs 0%, $P = .006$). Interestingly, IIEF scores decreased as a function of severity of semen quality impairment. Similar results were reported in a three-group study comparing azoospermic men, men with a sperm count < 15 mil/ml and men with sperm count > 15 mil/ml.[15] The direct correlation between semen quality and EF could be the consequence of an adverse emotional reaction to severe seminal abnormalities; however, it could be

Table 1. Studies assessing ED among male partners of infertile couples

	Study Design	Patients	Modality of ED assessment	Rate of ED	Main Finding	LoE
Coward et al.[35,*]	RCT	708 men with unexplained infertility	IIEF	9% reported ED	The Fertility Quality of Life score was inversely associated with ED	1b
Gabr et al.[14]	Case-control	1) 200 men of infertile couples 2) 200 controls	IIEF-5	ED was higher in the infertile group (52.5% vs 19%, *P* value: 0.001) Mild (SHIM 17-21): 29% Mild to moderate (SHIM 12-16): 22% Moderate (SHIM 8-11): 0.5% Severe (SHIM 5-7): 1%	Husband erectile score was significantly lower in the infertile group	3
Kizilay et al.[15]	Case-control	1) 57 azoospermia 2) 41 sperm count <15 million/mL 3) 81 sperm count >15 million/mL	IIEF	IIEF score: Group 1: 18,78 Group 2: 22,64 Group 3: 26,45	Positive correlation between sperm parameters and IIEF score	3
Sahin et al.[16]	Case-control	1) 39 primary infertile men 2) 31 secondary infertile men	IIEF	IIEF score Group 1: 27.7 Group 2: 24.4	IIEF scores of the primary infertile group was significantly higher than the secondary infertile group (*P* = .002).	3
Lotti et al.[17]	Case-control	1) 448 men of infertile couples 2) 74 age-matched fertile men	IIEF	Group 1: 18.3% reported ED (IIEF-EF score <26). - Mild: 11.8%, - Mild to moderate: 3.6%, - Moderate 1.8%, -Severe: 1.1% Group 2: 0%	ED prevalence increases as a function of semen quality impairment severity (*P* < .0001)	3
Ozkan et al.[18]	Case-control	1) 56 infertile men undergoing in vitro fertilization therapy 2) 48 fertile men	IIEF	Group 1) 84.9% mild-to-moderate erectile dysfunction Group 2) 100% mild-to-moderate erectile dysfunction	Being infertile did not cause significant impairment in EF compared to the control group	3
Gao et al.[19]	Case-control	1) 1,468 infertile men 2) 942 fertile men	IIEF-5	Group 1) ED: 18.05% Group 2) ED: 8.28%,	The incidence of ED was higher than those in the control group	3
Marci et al.[20]	Case-control	Group A: 30 diagnosed infertile couples	IIEF	26.6% in Group A, 6.66% in Group B and 0% in Group C		3

(continued)

Table 1. Continued

	Study Design	Patients	Modality of ED assessment	Rate of ED	Main Finding	LoE
		Group B: 30 infertile couples Group C: 52 co-habitant couples in fertile age			Group A male partners obtained lower scores in all the subscales	
O'Brien et al.[21]	Case-control	302 infertile men and 60 controls men (fertility seeking vasectomy)	Androgen Deficiency in the Aging Male and IIEF-5 questionnaires	38% reported significant andropause symptoms and 28% had abnormal IIEF-5 scores	Hypogonadal symptoms and ED are common among infertile men	3
Cao et al.[22]	Cross-sectional single arm	480 intertile men	IIEF-5	55%	Anxiety and depression were both associated with ED in infertile men	4
Akbal et al.[27]	Cross-sectional single arm	66 infertile men submitted to TESE	IIEF-5	19.6%	Unsuccessful TESE procedures might have a negative effect on EF because of hormonal and psychological reasons	4
Saleh RA et al.[23]	Cross-sectional single arm	412 infertile men	IIEF-5	11% experienced problems with erection or orgasm and had severe anxiety	Some men may experience sexual dysfunction of a psychogenic nature in response to the diagnosis of infertility	4
Khademi et al.[24]	cross-sectional single arm	100 men of infertile couples	IIEF	ED: 61.6% Severe ED: 2% Moderate ED: 5.1% Mild to moderate ED: 22.2% Mild ED: 32.3%	The prevalence of any degree of ED was higher than the prevalence reported for normal population and infertile men.	4
Jain et al.[25]	Cross-sectional single arm	175 infertile couples	Non-validated questionnaire	15%	Amongst the males, premature ejaculations was the most common problem	4
Elia et al.[26]	Cross-sectional single arm	171 male partners of sub fertile couple	IIEF	23.7%	There was no significant variation in the prevalence of sexual dysfunction related to seminal profile	4
Sahebalzamani et al.[28]	Cross-sectional single arm	193 infertile couples	IIEF	30.1%	Greater health literacy was associated with higher levels of sexual function and sexual satisfaction	4

(continued)

Table 1. Continued

	Study Design	Patients	Modality of ED assessment	Rate of ED	Main Finding	LoE
Yang et al.[29]	cross-sectional single arm	4,299 men of infertile couples	IIEF-5	Over all 57.8% Mild: 34.9% Mild to moderate: 9,8% Moderate: 10,5% Severe: 2,6%	Secondary infertility, infertility with known causes, and chronic prostatitis were significant risk factors associated with ED	4
Song et al.[30]	Cross-sectional single arm	260 male of infertile couples	IIEF-5	41.5% mild ED 10.4% greater than mild ED	ED was found to be common in the male partners of infertile couples	4
Seung-Hun et al.[31]	cross-sectional single arm	236 men of infertile couples	IIEF-5	Mild ED 42% Mild to moderate 7.6% Moderate to severe 1.3%	ED was found to be common in the male partners of infertile couples	4
Satkunasivam et al.[32]	cross-sectional single arm	1,750 men presenting for evaluation of infertility	IIEF-5	ED 30.5% Severe ED 1.3% Moderate ED 8.5% Mild ED 20.7%	The significant prevalence of symptoms of ED (31%) identified in this population highlights the importance of screening	4
Lotti et al.[5]	Cross-sectional single arm	244 men with couple infertility	IIEF	ED was found in 43 (17.8%) and PE in 38 (15.6%) subjects	ED is associated with depressive symptoms, while PEDT score is associated with prostatitis symptoms and signs, phobic anxiety, and free T	4
Shindel et. al.[33]	Cross-sectional single arm	121 infertile couples	IIEF	18% had mild ED and 4% had moderate ED	Depression, ED and sexual relationship problems are prevalent among male partners of infertile couples	4
Hammoud et al.[34]	Cross-sectional single arm	526 infertile couples	Not reported	9% reported ED	The incidence of erectile dysfunction did not vary across BMI categories when corrected for potential contributing factors.	4

*The trial was not designed to assess ED prevalenceED = Erectile dysfunction; IIEF = International Index of Erectile Function

also the mirror of an overall poorer health status. Indeed, both ED and MI are significantly associated with a higher comorbidity burden.[36–38] In line with this theory, Lotti et al observed that men with worse semen parameters and EF were also less healthy as assessed with the Chronic Disease Score.[17]

The psychological distress associated with the inability to conceive and the consequent perceived loss of masculinity are putative factors for ED among infertile men.[39] Depressive symptoms have been frequently associated with worse EF parameters in infertile men[5,22,23,40]: in a cohort of infertile men, Lotti et al.[5] showed that depression was the only factor significantly associated with ED, after adjusting for confounding factors (OR = 1.19 [1.02 - 1.39]). Moreover, the same group in another study reported that EF was significantly associated with overall psychological burden and particularly with somatized anxiety[17]

Ozkan et al.[18] published the only study concluding that being infertile did not cause significant impairment of EF. They compared 56 infertile men from couples undergoing in vitro fertilization and 48 fertile men. Mild-to-moderate ED was detected in 85.9% of men from the infertile group and in 100% of the control group according to IIEF-5. The high rate of ED observed in both groups could be the consequence of a possible bias in patient selection.

2. Treatment

PDE5is are considered the first line therapy for ED according to international clinical guidelines.[41] Overall, 11 RCTs and one open-label prospective study investigated the safety and efficacy of PDE5is for the treatment of ED in male partner of infertile couples (Table 2).[42–53] The clinical interest was driven by preclinical evidence showing a possible interaction of certain isoforms of PDE enzymes in different steps of semen production and ejaculation.[54] Aversa et al.[42] investigated, for the first time in a double-blind randomized fashion, the effect of one single dose of 100 mg sildenafil on semen parameters in 20 healthy men vs. placebo. They showed no changes in seminal parameters after treatment. Similar results were reported by other authors.[43] Interestingly, Pomara et al.[48] conducted a small RCT to investigate the effect of a single dose of sildenafil 100 mg vs. tadalafil 20 mg in 18 young infertile men. They reported an increase in sperm progressive motility after sildenafil (median value 37% vs. 28.5%) as compared to baseline, thus confirming previous findings showing increased sperm kinematical parameters after single dose of 50 mg sildenafil.[47] Similarly, the effect of tadalafil on sperm parameters was investigated in several trials.[44–46,50,53] In a large RCT, Hellstrom et al.[46] tested the effect of daily administration of tadalafil 10 or 20 mg vs. placebo in 421 healthy men. Semen parameters were analyzed after 6 months of treatment and compared to baseline. In the latter study, the authors did not find any impact of tadalafil on spermatogenesis and serum reproductive hormones. The authors confirmed the same results in a different cohort of patients older than 45 years.[50] In an another placebo-controlled RCT including 20 infertile men with diabetes mellitus and ED, total sperm count, progressive motility and ejaculate volume were even improved by tadalafil 5 mg daily for 3 months when compared to placebo.[53] Conversely, in the aforementioned study comparing 100 mg sildenafil vs. 20 mg tadalafil, Pomara et al.[48] reported decreased sperm progressive motility after tadalafil as compared to baseline (median value 21.5% vs. 28.5%). A positive effect of PDE5is on semen parameters was also reported in RCTs investigating the effect of vardenafil vs. placebo.[49,51] In a cohort of 205 infertile men a single daily dose of vardenafil 10 mg taken for 15 days led to a significant improvement in sperm forward motility, semen volume and concentration as compared with baseline.[49] In a recent meta-analysis pooling data from 11 RCTs, including 1,317 patients, the authors reported that acute administration of PDE5is had no effect on semen volume (Mean difference = 0.26; 95% CI: 0.00-0.48) and sperm concentration [Mean difference = 2.04; 95% CI: -2.95 to 7.04], while the rate of motile sperm (Mean Difference = 7.05; 95% CI: 2.59-11.51), total progressive motility (Mean Difference = 6.23; 95% CI: 2.43-10.04), and rapid progressive motility (Mean Difference = 3.11; 95% CI: 0.23-5.99) were increased after PDE5is administration.[55] Interestingly, these results were significant only in infertile men, suggesting that at least part of the effect could be caused by normal variation and regression toward the mean.

Overall, these findings confirm the safety of PDE5is use among patients seeking fatherhood, with few data suggesting a possible positive effect on semen parameters. Beside that, the expected positive effect of PDE5is on EF was also confirmed in this specific population.

Surprisingly, only one study investigated the impact of treatments other than PDE5is on EF.[56] Kobori et al[56] evaluated the effectiveness of antioxidant co-supplementation therapy in 47 adult men with OAT and mild ED. The patients were treated with a combination of L-arginine 690 mg and French maritime pine bark extract (Pycnogenol) 60mg. The authors concluded that after 4 months, the treatment was associated with statistically significant improvement in total IIEF score (57.69 ± 11.04 to 59.43 ± 12.57). The sperm concentration was also enhanced significantly after both 2 and 4 months of treatment (11.79 ± 9.86 to 21.22 ± 28.17 and 20.15 ± 23.99 mil/ml). However, the study did not show improvement in the IIEF-EF domain and without a control group, the improvements in both sexual function score and semen parameters may represent a placebo effect and natural variation.

VALUES

Several studies have demonstrated a relatively high prevalence of ED among male patients of infertile couples. Due to the lack of prospective trials, it is not possible to establish a cause-and-effect relationship. However, the observed association between depressive symptoms and anxiety and ED detected in men from infertile couples indicates that underlying mechanisms may be,

Table 2. Studies assessing ED treatment among male partners of infertile couple

	Study Design	Patients	Investigated treatment	Main Finding	LoE
Aversa et al.[42]	RCT	20 healthy men	Sildenafil 100 mg single dose vs Placebo	Sildenafil caused no changes in seminal parameters when compared to placebo	1
Purvis et al.[43]	RCT	17 healthy men	Sildenafil 100 mg vs. placebo single dose for two periods with 5-7 days between doses	These results indicate that a single 100-mg oral dose of sildenafil does not have an adverse effect on sperm function or ejaculate quality.	1
Yang et al.[44]	RCT	20 asthenozoospermic vs. 20 normozoospermic	Tadalafil 20 mg vs. sildenafil 100 mg 1 dose	After the administration of tadalafil (2 h) and sildenafil (1 h), there was no significant difference in semen parameters and in premature acrosome reaction incidence rate.	1
Corvasce et al.[45]	Prospective single-arm	27 men unaware of fertility status	Tadalafil 5 mg daily for three months.	Tadalafil improved sperm motility (52.94 % vs. 57.59%); normal morphology (48.91% vs. 54.74%) and semen volume (1.97 vs. 2.38) compared to baseline.	3
Hellstrom et al.[46]	RCT	421 healthy men	Tadalafil 10 mg daily vs. tadalafil 20 mg daily vs. placebo for 6 months	Chronic daily administration of tadalafil at doses of 10 and 20 mg for 6 months had no adverse effects on spermatogenesis	1
du Plessis et al.[47]	RCT	20 healthy men	50 mg sildenafil 1 dose vs. placebo	Sildenafil citrate treatment had no effect on both macroscopic and microscopic seminal parameters as well as the acrosome reaction. However, sperm-zona pellucida binding results were increased to 148.75%	1
Pomara et al.[48]	RCT	18 infertile men	Sildenafil 50 mg vs. tadalafil 20 mg 1 dose.	Significant increase in sperm progressive motility (median value, 37.0% vs. 28.5%) was observed after sildenafil administration as compared with baseline; in contrast, a significant decreased in semen parameters was observed after tadalafil (median value, 21.5% vs. 28.5%).	1
Jarvi et al.[49]	RCT	200 healthy men	Vardenafil 20 mg daily vs. sildenafil 100 mg daily vs. placebo for 6 months	Vardenafil had no adverse effects on sperm concentration, compared with sildenafil and placebo	1
Hellstrom et al.[50]	RCT	253 healthy men	Tadalafil 20 mg daily vs. placebo for 9 months	This study demonstrated no deleterious effects of 9 months of daily tadalafil 20mg on spermatogenesis or hormones related to testicular function	1
Dimitriadis et al.[51]	RCT	75 men with oligoasthenospermia	Vardenafil 10 mg daily (group A) vs. sildenafil 50 mg daily (group B) vs. l-carnitine	Increase in sperm concentration (Group A: 10.6 vs. 22.6; Group B: 9.5 vs. 24.3) percent of motile sperm (Group A: 19.3 vs. 39.2; Group B: 25.7 vs. 47.1) and percentage of	1

(continued)

Table 2. Continued

	Study Design	Patients	Investigated treatment	Main Finding	LoE
			(group C) vs. no treatment (group D) for 12 weeks	morphologically normal sperm (Group A: 24.3 vs. 40.6; Group B: 23.6 vs. 41.3)	
Rago et al.[52]	RCT	205 infertile men	Vardenafil 10 mg 1 dose (group B) vs. vardenafil 10 mg every other day for 15 days (group C) vs. placebo (group A)	Significant increase in percentage forward motility after vardenafil administration compared to baseline (Group B: 14.1% vs. 21.8%; Group C: 13.8% vs. 22.7%) In group C, there was an increase in the mean semen volume (3.0 mL vs. 3.4 mL) and an improvement in the mean total sperm concentration (37.0% vs. 76.1%) as compared with baseline.	1
La Vignera et al.[53]	RCT	20 infertile patients with symptomatic diabetic neuropathy and ED	Daily administration of 5 mg tadalafil for 3 months vs. placebo	Patients showed a significant increase in seminal vesicles ejection fraction and a significant improvement in total sperm count, progressive motility, seminal levels of fructose, leucocytes and ejaculate volume.	1
Tan et al.[55]	Meta-analysis	1317 patients	PDE5is	Acute administration of PDE5is had no effect on semen volume (MD = 0.26; 95% CI: 0.00-0.48) The percentage of motile spermatozoa (MD = 7.05; 95%CI: 2.59-11.51), total progressive motility (MD = 6.23; 95%CI: 2.43-10.04), rapid progressive motility (MD = 3.11; 95%CI: 0.23-5.99) and of morphologically normal spermatozoa (MD = 12.15; 95%CI: 5.16-19.15) were increased after oral PDE5 inhibitors treatment in infertile men.	1
Kobori et al.[56]	Prospective single-arm	47 men with OAT syndrome	Combination of L-arginine (690 mg) and French maritime pine bark extract (60mg)	The sperm concentration was enhanced significantly after treatment 2 and 4 months (11.79 ± 9.86 to 21.22 ± 28.17 and $20.15 \pm 23.99 \times 106$/ml). Significant improvements in the IIEF were observed in the total score of IIEF (57.69 ± 11.04 to 59.43 ± 12.57) after 4 months of treatment	3

IIEF = International Index of Erectile Function; OAT = oligo asthenotera tozoospermia; PDE5i = phosphodiesterase type 5 inhibitors; RCT = randomized clinical trial

at least partially, explained by the psychological distress caused related to the fertility problem. In addition, case-control studies have indicated that in some cases a correlation between MI and ED could have a biological background as EF seem to worsen along with semen parameters.

Several RCTs provided LoE 1 regarding the safety of PDE5is for the treatment of ED in infertile men and some studies even indicate that the medication may improve semen parameters.

REMARKS

The majority of studies provided low LoE on the association between ED and infertility. Moreover, current data do not allow determining the actual impact of ED on male reproductive outcomes. In spite of this, it seems clear that men from infertile couples should be screened for sexual dysfunctions and offered treatment if this is present.

Data showing a possible improvement in seminal parameters after PDE5is treatment are controversial, thus hampering to draw conclusions on the positive effects of PDE5is on male reproductive potential.

Testosterone is crucial for erectile function acting either at central and peripheral level[57,58] Testosterone replacement therapy can improve several aspects of male sexual function in hypogonadal men.[57,58] However, it should be recognize that TRT is contraindicated in men seeking medical care for couple infertility since it can further worse seminal parameters. The use of hCG or selective estrogen receptor modulators (SERMs) can represent a good alternative in the presence of secondary hypogonadism.[59] However, no specific study has evaluated the sexual outcomes of the later drugs in the infertile population.[8] Hence, further studies are advisable in order to better investigate this issue.

EJACULATORY DYSFUNCTIONS

Statements

1 Prevalence and association
- Male partners of infertile couples are at higher risk of reporting PE (Level 3; Grade C)
- Further studies are needed to determine the prevalence of RE and anejaculation among male partners of infertile couples

2 Treatment
- Penile vibratory stimulation (PVS) and electroejaculation (EEJ) are effective treatments for anejaculation in infertile men (Level 2; Grade B)
- PVS seems more effective using a frequency of 100 Hz an amplitude of 2.5 mm compared to an amplitude of 1 mm (Level 2; Grade B).
- Medical treatment of RE in infertile men with pseudoephedrine, amoxapine or imipramine can provide antegrade ejaculates although larger trials are needed (Level 3; Grade C)
- Further studies are needed to determine optimal treatment of PE among infertile men,

Evidence

1. Prevalence and association

Epidemiological studies of EjDs among infertile men are limited. Currently, three case-control studies[5,19,60] and six single-arm studies[17,22,40,61–63] have investigated PE among infertile men; one case-control[64] and one single-arm study[65] have looked at RE, while only one study have investigated the prevalence of anejaculation among infertile men[10] (Table 3).

Of the studies investigating PE, four used the Premature Ejaculation Diagnostic Tool (PEDT) and defined PE as a PEDT score > 8. The largest of these is a Chinese case-control study including 1,468 men of infertile couples aged 23 to 45 years and 942 voluntary fertile controls with at least one child.[19] The prevalence of PE in infertile vs. fertile men was 19.01% vs. 10.93% ($P < .001$). The study also evaluated Intravaginal Ejaculation Latency Time (IELT) and found that a large amount of infertile men when compared to fertile subjects had an IELT < 1 minute (11.24% vs. 7.75%, $P < .001$). The other case-control study using PEDT compared 448 men from infertile couples with a mean age of 36.8 years and 74 age-matched healthy fertile controls and found that 12.9% of males from infertile couples had PE vs. 4.1% of fertile men ($P = .036$).[17] Interestingly, the study found that azoospermic men had the highest prevalence of PE. In a retrospective cohort study from the same group, the prevalence of PE, based on PEDT, among 244 infertile men was 15.6% with 38.5% reporting lifelong PE and 61.5% reporting acquired PE.[5] In the same study patients with PE were more likely to report prostatitis symptoms. In this context prostatitis symptoms have been frequently associated with PE in several studies[66]; considering that male accessory gland infection and inflammation could be a reason for semen impairment, patients with this condition could be at higher risk of reporting both PE and fertility issues.

Smaller studies report varying prevalence of PE depending on the applied definition. Using a self-designed non-validated questionnaire, a cross-sectional study including 300 infertile men aged 30.4 years found a PE prevalence of 43% with 74.4% reporting lifelong PE and 25.6% reporting acquired PE.[61] Another cross-sectional study defining PE based on interviews of sexual performance found a PE prevalence of 14.9% among 268 men form infertile couples.[62] Furthermore, a prospective cohort study found a rate of 50% among 73 men from infertile couples based on a five-item patient and partner-specific questionnaire related to PE.[40] Finally, two studies investigated the prevalence of PE among men with Klinefelter Syndrome (KS). The first is a case-control study including 53 KS patients and 75 age-matched infertile men without KS.[60] Based on the Arabic index for PE (AIPE ≤ 30) 22.6% of the KS patients had PE compared to 45.3% of the age-matched group ($P < .05$). The second is also a case-control study involving 21 men with KS and 1,365 men attending an outpatient clinic for sexual dysfunction. The definition of PE was ejaculation occurring always or nearly always prior

Table 3. Studies assessing EjDs among male partners of infertile couples

Study	Study Design	Patients	Modality of assessment	Rate of EjD	Main Finding	LoE
Premature ejaculation						
Cao et al.[22]	Prospective cohort	480 infertile men seeking treatment	PEDT (PEDT score >8)	86/440 (19.5%) had PE	Anxiety but not depression is associated with PE	3
Lotti et al.[17]	Case-control	448 infertile men and 74 age-matched healthy fertile controls	PEDT (PEDT score >8)	12.9% of males from infertile couples had PE vs. 4.1% of fertile men had PE (P = .036)	Azoospermic men reported higher PE prevalence	3
El Bardisi et al.[60]	Case-control	53 men with Klinefelter Syndrome (KS) and 75 age-matched infertile men without KS	Arabic index for premature ejaculation (AIPE) (AIPE is ≤30)	12/53 (22.6%) of KS men had PE vs. 34/75 (45.3%) controls (P < .05)	The prevalence of PE in KS men is significantly lower compared to age-matched infertile men without KS.	3
Gao et al.[19]	Case-control	1468 infertile men and 942 fertile controls	PEDT (PEDT score >8) IELT	PE based on PEDT: 19.01% vs.10.93%, P < .001 IELT: <1min: 11.24% vs. 7.75% 1 ≤ 2 min: 18.80% vs. 13.69%	Infertile men reported higher rates of anxiety and depression.	3
Lotti et al.[5]	Cross-sectional single arm	244 infertile men	PEDT (PEDT score >8)	PE in 38/244 (15.6%) of infertile men Among these, 38.5% had lifelong PE and 61.5% acquired PE	ED and PE are reported by one in six infertile patients.	4
Hassanzadeh et al.[61]	Cross-sectional single arm	300 infertile men	Self-designed, non-validated questionnaire	43% of patients had PE Among these, 74.4% had lifelong PE and 25.6% acquired PE 51.2% of patients with PE reported time to ejaculation less than 1 min	High frequency of PE among infertile men.	4
Omu et al.[62]	Cross-sectional single arm	268 infertile men	Interview on sexual performance	PE in 40/268 (14.9%)	Reports specific causes of male infertility and emotional responses.	4
Corona et al.[63]	Retrospective cohort	21 men with KS	PE defined as ejaculation occurring always or nearly always prior to or within about 1 min	2/21 (9.5%) had PE	Sexual dysfunction in KS is caused by the underlying hypogonadal state	4
Shindel et al.[40]	Prospective cohort	73 infertile men	Five-item patient and partner-specific questionnaire related to PE	50% reported PE	Self-reported PE is prevalent among infertile men. PE is associated with lower relationship satisfaction in both men and women.	4

(continued)

Table 3. Continued

Study	Study Design	Patients	Modality of assessment	Rate of EjD	Main Finding	LoE
Retrograde ejaculation						
Mieusset et al.[64]	Case-control	245 infertile men with semen volume < 2ml and 162 infertile men with a semen volume > 2ml	Post-ejaculatory urine test	15/245 (6%) of infertile men with semen volume < 2 ml had sperm in post-ejaculatory urine vs. 12/162 (7%) of infertile men with semen volume > 2 ml	-	3
Lee et al.[65]	Retrospective cohort	920 infertile men, 96 of them azoospermic	Not specified	4/96 (4%) azoospermic men had RE	Identification of specific causes of male infertility is presented	4
Anejaculation						
Punab et al.[10]	Prospective single arm	1737 infertile men	Post-ejaculatory urine test	Retrograde Ejaculation 2.2% Anejaculation 1.2%	-	3

AIPE = Arabic index of premature ejaculation; IELT = intravaginal ejaculatory length of time; PE = premature ejaculation; PEDT = premature ejaculation diagnostic tool; RE = retrograde ejaculation; SCI = spinal cord injury

to or within about 1 minute. A total of 2/21 of the KS men (9.5%) had PE and after adjustment for age with no difference when compared to controls.

Only two studies investigated RE rate among infertile men. In a case-control study comparing 245 infertile men with a semen volume < 2 ml with 162 infertile men with a semen volume > 2 ml, 6% vs. 7% had sperm in the post-ejaculatory urine sample and was diagnosed with RE.[64] In a retrospective cohort study, involving 920 infertile men, RE was found in four (4%) out of 96 of azoospermic subjects.[65]

Regarding anejaculation, Punab et al.[10] showed that, in a large prospective clinical-epidemiological study investigating causes of male infertility, anejaculation accounted for 1.2% of all causes. Spinal cord injury (SCI) was the main cause of anejaculation accounting for 65% of cases, followed by diabetes mellitus and multiple sclerosis. Interestingly, in up to 15% of patients with anejaculation no organic cause was detected, thus suggesting a possible psychogenic etiology[10]

2. Treatment

The majority of studies investigating treatment of EjDs in infertile men are dealing with anejaculation or RE (Table 4). Conversely, we identified only three studies specifically addressing possible improvement in PE among infertile men affected by varicocele.

In a prospective study, the authors investigated the effect of varicocelectomy on PE in a cohort of infertile men with both varicocele and PE.[67] The working hypothesis being that reducing blood refluxing would increase fertility and improve PE.[68,69] A total of 51 men underwent varicocelectomy which resulted in a significant increase in IELT ($P < .05$). No sperm counts were reported. The effect of varicocele treatment on PE have been investigated in other two studies[70,71]; however, both of them were conducted on patients with semen impairment but no evidence of couple infertility and for this reason they will not be taken in account in our analysis.

Several medical approaches have been investigated in order to achieve antegrade ejaculation for natural reproduction in patients with RE. The tested substances include imipramine (tri-cyclic antidepressant), amoxapine (tri-cyclic antidepressant), B12 vitamin, pseudoephedrine (stimulation of α and β receptors in the urinary tract) as well as injection of collagen within the bladder neck.[72–76] One cross-over RCT treated 26 patients with amoxapine (50 mg daily) and B12 vitamin (500 ug 3 times per day), separately for a period of 4 weeks with each drug.[73] Amoxapine, which acts as a noradrenaline re-uptake inhibitor, was effective in 80% of patients compared to only 16% success obtained in the vitamin B12 group. In another study, comparing the effects of imipramine 25 mg twice per day and pseudoephedrine 120 mg twice per day on RE in diabetic men, Arafa et al.[75] found a more moderate success rate of 38.5% with imipramine. However, the use of pseudoephedrine resulted in almost half of the patients having antegrade ejaculation and this increased to 61.5% when combining the two drugs. Of note, the side-effects of sympathomimetics include dryness of mucous membranes and

Table 4. Treatment of EjDs in male partners of infertile couples

Study	Study Design	Patients	Investigated treatment	Main Finding	LoE
PE					
Hosseini et al.[67]	Prospective clinical trial	51 infertile men with PE and clinical grade 2 or 3 varicocele	Microsurgical varicocelectomy	Statistically significant increase in urine Dopamine levels one month after varicocelectomy	3
RE					
Shoshany et al.[72]	Retrospective cohort	20 men with RE (12 complete, 8 partial)	60mg pseudoephedrine every 6 h on the day before semen analysis and 2 × 60 mg on the day of semen analysis	7/12 (58%) complete RE recovered spermatozoa in an antegrade ejaculate 5/8 partial RE had ≥ 50% increase in antegrade total sperm count	3
Hu et al.[73]	RCT	26 men with complete RE (13 in each group)	Amoxapine 50mg daily for 4 weeks → 1 week washout → Vit B12 500ug 3 times per day for 4 weeks Crossover to: Vit B12 500 ug 3 times per day for 4 weeks → 1 week washout → Amoxapine 50mg daily for 4 weeks	Antegrade ejaculation during treatment: Amoxapine: 20/25 (80%) Vit B12: 4/25 (16%)	2
Kurbatov et al.[74]	RCT	24 men with complete RE due to DM1 refractory to Imipramine (12 in each group)	Endourethral collagen injection vs. endourethral saline injection	Better antegrade volume after collagen injection (mean difference: 0.71ml, $P < .05$)	2
Arafa et al.[75]	Prospective clinical trial	33 RE patients due to diabetes (23 complete, 10 partial)	Three sequential courses: Imipramine 25 mg twice/day, pseudoephidrine 120 mg twice/day, or combination of the two drugs.	Antegrade ejaculate in complete RE: - imipramine 10 patients (38.5%) - pseudoephedrine 11 patients (47.8%) - both drugs together 16 patients (61.5%) Partial RE: significant increase in semen parameters in all groups	3
Ochsenkühn et al.[76]	Retrospective cohort	11 men with RE due to retroperitoneal surgery (7 complete, 4 partial)	Imipramine: increasing from 25 to 50 mg for 7 days prior to the planned	Antegrade ejaculate obtained in all men	3

(continued)

Table 4. Continued

Study	Study Design	Patients	Investigated treatment	Main Finding	LoE
			ejaculation or expected ovulation of female partner		
Anejaculation					
Meng et al.[77]	Retrospective cohort	20 men with psychogenic anejaculation refractory to PVS	EEJ	Successful retrieval in all men	2*
Soeterik et al.[78]	Retrospective cohort	47 SCI men	EEJ	Spermatozoa found in 199/230 EEJ attempts (86.5%)	2*
Castle et al.[95]	Prospective cohort	30 SCI men	PVS	Successful retrieval in 23/30 (76.7%) of the men	2*
Meng et al.[98]	Case-control	91 idiopathic anejaculation vs. 60 healthy fertile controls	In the anejaculatory group: A stepwise approach using nocturnal emission (NE), PVS and EEJ In the control group: masturbation	Successful retrieval in all men (10 from NE, 40 from PVS, 41 from EEJ and from masturbation in all 60 controls)	4
Gat et al.[88]	Retrospective cohort	15 men with psychogenic anejaculation and 22 SCI men	EEJ	Successful retrieval in all men	2*
McGuire et al.[89]	Retrospective cohort	31 SCI men	EEJ	Successful retrieval in all men	2*
Das et al.[91]	Retrospective cohort	16 SCI men	Repeated EEJ to improve semen parameters	No improvement in volume, concentration, motility or total motile count in successive antegrade and retrograde samples following repeated EEJ	2*
Hovav et al.[92]	Retrospective cohort	59 neurologically intact men with anejaculation	Repeated EEJ to improve semen parameters	No improvement on repeated samples except for antegrade volume (0.33 +/- 0.16 ml)	2*
Hovav et al.[93]	Retrospective cohort	25 men with psychogenic anejaculation	EEJ	Successful retrieval in all men	2*
Ohl et al.[94]	Retrospective cohort	121 men with anejaculation (118 neurogenic, 3 psychogenic)	EEJ	52 couples became pregnant (43%)	2*
Heruti et al.[79]	Retrospective cohort	84 SCI men	EEJ	Successful retrieval in all men	2*
Schatte et al.[80]	Prospective cohort	17 men with anejaculation (10 SCI, 5 RPLND, 2 idiopathic)	EEJ	Successful retrieval in all men	2*

(continued)

Table 4. Continued

Study	Study Design	Patients	Investigated treatment	Main Finding	LoE
Chung et al.[81]	Retrospective cohort	13 anejaculatory men (7 RPLND, 1 SCI, 5 psychogenic)	EEJ	Successful retrieval in all men	2*
Brackett et al.[96]	Retrospective cohort	211 SCI men	PVS	Retrieval rates: High amplitude (2.5mm) 54.5% Low amplitude (1mm) 39.9% Ejaculatory success highest in C3-C7 followed by T1-T5, T6-T10 and T11-L3.	2*
Chung et al.[86]	Retrospective cohort	26 men with anejaculation (23 SCI, 3 RPLND)	EEJ	77/84 (91.6%) of EEJ procedures successful defined by at least 10mio sperm found	2*
Hulting[82]	Retrospective cohort	10 men with anejaculation/ RE due to treatment of testis cancer	EEJ	Successful retrieval in 9/10 (90%) of the men	2*
Sønken et al.[97]	Prospective clinical trial	66 SCI men	PVS with 1mm or 2.5mm amplitude	Retrieval rates: In the first group (n=25): 1mm = 32% 2.5mm = 96% In the second group (n=41): 2.5mm = 83%	2*
Wang et al.[83]	Retrospective cohort	25 SCI men	EEJ	Successful retrieval in 22/25 (88%) of the men: Bi-directional emission was found in 12 patients, antegrade in nine, retrograde in one and failure in three.	2*
Denil et al.[84]	Retrospective cohort	198 men with anejaculation	EEJ	At least 10 mio progressively motile sperm was obtained in: - 75% of SCI men - 87% of men following RPLND	2*
Lucas et al.[85]	Retrospective cohort	14 anejaculatory men	EEJ	Successful retrieval in 21/26 (80.8%) of the men	2*

*Studies showing a dramatic effect of the investigated treatmentEEJ = electroejaculation; PE = premature ejaculation; PVS = penile vibratory stimulation; RE = retrograde ejaculation; SCI = spinal cord injury

hypertension. Exploring a different approach to the problem, Kurbatov et al. injected collagen into the bladder neck to increase the constriction of the internal sphincter.[74] A total of 24 diabetic men were randomized to either a collagen or a saline injection, showing a small increase in antegrade ejaculate with a mean difference of 0.71 ml in favor of patients receiving collagen ($P < .05$).

In general, EEJ[77–94] and PVS[95–97] are the two treatment options investigated for sperm retrieval in men with anejaculation. Retrieval rates with EEJ have been reported to range between 75% and 100%, mainly depending on whether the outcome measure was simply sperm retrieval or a specific quantity of motile sperm.[78,79,81,84] In this context, results from a retrospective study, including 84 men with SCI, showed that when stimulated with a rectal probe EEJ, 98.6% of the patients achieved ejaculation and motile sperms were found in 88.1% of the samples.[79] In a similar cohort of 198 men including both SCI and retroperitoneal lymph node dissection (RPLND) as causes for anejaculation, Denil et al.[84] obtained ejaculates with EEJ with sperm counts of > 10 mil/ml in 75% and 87% of the SCI and RPLND group, respectively.

Three studies have investigated success rates with vibratory stimulation of the dorsal penile nerve and achieved successful retrieval in 32% to 96% of the patients.[95–97] Success was primarily dependent on amplitude of the stimulation. In a cohort of 66 men with SCI and anejaculation, Sønksen et al.[97] found better success rates with a 100 Hz frequency and an increasing amplitude of the stimulation plate spanning from 32% with an amplitude of 1 mm, to 96% with an amplitude of 2.5 mm. In a similar setting with 211 SCI men, Brackett et al.[96] managed good results using an amplitude of 2.5 mm, resulting in sperm retrieval in 54.4% of the cases. Interestingly, there seem to be a better sperm quality with PVS as compared to EEJ.[98]

Values

Based on the limited epidemiological evidence using validated tools to investigate PE among infertile men, we found that male partners of infertile couples are at higher risk of reporting PE, which is likely to be associated with increased psychological distress of men from infertile couples. Only two observational studies reported RE among infertile men, while no studies investigated the prevalence of anejaculation among infertile men.

Case-control and single-arm trials have produced convincing results on PVS and EEJ for the treatment of anejaculation in infertile men. Of note, these procedures are not devoid of side effects including skin abrasion, penis edema, and autonomic dysreflexia in men with a history of SCI. However, these potential side-effects can be safely mitigated by observing the penile skin during PVS and by pre-treating men prone to autonomic dysreflexia with antihypertensive medication such as nifedipine.[99] Medical treatment of RE in infertile men have been investigated in RCTs with pseudoephedrine, amoxapine or imipramine showing positive results. In case of treatment failure, sperm retrieval from alkalinized urine represents a valuable option.[2] However, the number of patients studied is limited and the quality of the available studies is overall poor. Further studies are needed to determine optimal treatment of PE among infertile men.

REMARKS

Although PE seems more prevalent among men from infertile couples, available studies are heterogeneous in the definition of PE and in the population characteristics. Further, few studies were specifically aimed to investigate the prevalence of PE among infertile men. Only two observational studies investigating RE among infertile men were available. Both suffer from selection bias, as one[64] selected patients based on ejaculate volume and the other[65] only reported RE among azoospermic men. Only one study investigated the prevalence of anejaculation in a cohort of unselected infertile men[10]

There is a shortage of RCTs investigating the treatment of anejaculation in infertile men and thus LoE 1 is currently lacking. Medical treatment of RE needs to be validated in larger cohorts.

LOW SEXUAL DESIRE

Statements:

1 Prevalence and association:
   - Male partners of infertile couples may suffer from LSD in about one third of cases. Patients with severe male factor infertility and longer duration of infertility are at higher risk of LSD (Level 3; Grade C)
2 Treatment:
   - Due to the lack of available data, no recommendation can be given on LSD treatment in male partners of infertile couples.

EVIDENCE

Epidemiological studies on LSD among infertile men are limited. Currently, four case-control studies[17,20,100,101] and six observational studies[24,26,102–105] have investigated the prevalence of LSD among men from infertile couples (Table 5).

Lotti et al.[17] compared 448 men of infertile couples with a mean age of 36.8 years and 74 age-matched healthy fertile controls. Infertile men were divided into a group of 96 azoospermic men, a group of 245 men with at least one semen alteration and a group of 107 men with normal semen parameters. Results showed that azoospermic men had significantly lower sexual desire compared to fertile controls according to the IIEF-Sexual Desire domain (7.4 vs 7.9; $P < .05$). There was no difference between the groups of infertile men with semen abnormalities or those with normal semen parameters as compared with the fertile controls. In another case-control study[100] including 61 men with non obstructive azoospermia, 69 with severe oligospermia and 60 fertile men, the authors found the prevalence of LSD (as assessed with a single question) to be 8%, 4%, and 0% respectively.

Table 5. Studies assessing LSD among male partners of infertile couples

	Study Design	Patients	Modality of SD assessment	Rate of LSD	Main Findings	LoE
van Zyl JA et al.[102]	cross-sectional single arm study	514 male patients of infertile couples	times out of 10 intercourse without libido (dichotomization not reported)	68.7%	—-	4
Giannouli C et al.[100]	case-control study	61 men with idiopathic non-obstructive azoospermia vs. with 69 men with known causes of infertility vs. 60 fertile men	not provided	8% in idiopathic NOA, 4% in infertile of known cause, 0% in fertile men	—-	3
Ramezanzadeh F et al.[103]	cross-sectional single arm study	200 men of infertile couples	Sexual desire graded in a 5-points Likert scale	N/R	- Longer duration of relationship, of history of infertility, of treatment for infertility and ageing correlated with worse sexual desire - greater coitus frequency, mutual understanding within the couple and present sexual satisfaction correlated with better sexual desire	4
Khademi A et al.[24]	cross-sectional single armstudy	100 male patients of infertile couples	IIEF-SD domain	N/R	– No relationship between degree of sexual desire and male or female age, duration of infertility, male education, type of infertility, family income.	4
Elia J et al.[26]	cross-sectional single arm study	156 men of infertile couples	IIEF-SD domain	N/R	- Significantly lower score in men having sex for reproduction than the same men having sex for pleasure and the same men having sex before starting to conceive a baby	4
Marci R et al.[20]	case-control study	30 men from infertile couples (recent diagnosis), 30 men from infertile couples (already undergoing IUI), 52 control with no history or suspicious infertility	IIEF-SD domain	N/R	– Significantly lower IIEF-SD score in infertile men as compared with controls – No difference in IIEF-15-SD scoree between men with recent or previous diagnosis of infertility	3

(continued)

Table 5. Continued

	Study Design	Patients	Modality of SD assessment	Rate of LSD	Main Findings	LoE
Bayar U et al.[104]	prospective study	55 male patients of infertile couples undergoing IUI	ASEX questionnaire dichotomized (threshold used 5) for low desire	Before IUI: 16% After IUI: 26%	—	3
Satkunasivam R et al.[32]	cross-sectional single arm study	1750 men evaluated for infertility	Androgen Deficiency in the Aging Male (ADAM)	26.6%	- Prevalence of 45.2% of androgen deficiency symptoms and 19.9% of ED in MI men with low libido - TT and BioT associated with low libido - Age, medications, DM and hypertension associated with low libido - PRL, E2 and gonadotropins not associated with low libido	4
Lotti F et al.[17]	case-control study	448 male patients evaluated for couple infertility + 74 fertile controls	IIEF-SD domain	N/R	– Significantly lower IIEF-SD score in azoospermic men as compared with fertile men. – No differences in IIEF-SD score between infertile men with at least 1 altered semen parameter or normozoospermic infertile men and controls	3
Purcell-Lévesque C et al.[105]	cross-sectional single-arm study	45 male partners from infertile couples	Arizona Sexual Experiences Scale	28.9%	No association with attachment anxiety or avoidance and HSDD in infertile men	4
Kruljac M et al.[101]	case-control study	165 subfertile men vs. 199 fertile men	Sexual Complaints Screener for Men (SCS—M)	N/R	OR for low desire in infertile men: - 2.1 (1.2-3.8) p=0.02 after infertility treatment - 1.1 (0.5-2.2) p=0.84 at the beginning of workup for infertility	3

ED = erectile dysfunction; IIEF = International Index of Erectile Function; SD = sexual desire

Marci et al.,[20] studied LSD in a group of 60 men of infertile couples compared to 52 male partners of women attending for routine gynecologic testing. Based on the IIEF-SD domain, sexual desire was significantly lower in men from the infertile couples compared to controls. A recent case-control study by Kruljac et al.[101] compared 165 men with sperm counts < 15 mil/mL and 199 fertile age-matched controls. The Sexual Complaints Screener for Men (SCS-M) was utilised. When compared to controls, LSD was significantly more prevalent among infertile hypogonadal men in comparison to fertile controls but not in infertile men who were eugonadal [OR (95% CI): 2.3 (1.0-5.5); $P = .05$ vs. 1.5 (0.89-2.7); $P = .12$]. In addition, LSD was significantly more reported by men who have completed infertility treatment rather than men at initial infertility screening [OR (95% CI): 2.1 (1.2-3.8); $P = .02$ vs 1.1 (0.5-2.2)].

Other observational studies described the prevalence of LSD in male partners of infertile couples. Using a specific questionnaire, Satkunasivam et al.[32] reported LSD in 26.6% of 1,750 men who presented for infertility evaluation at one center. Interestingly, although the authors reported a high prevalence of patients with low level of total or bioavailable T, suggesting androgen deficiency (45.2%), they did not find an association between total, bioavailable T levels and low libido. Therefore, the authors speculate that the high prevalence of low libido in their cohort was secondary to psychological factors associated with the stress and anxiety of infertility and infertility treatments. Another specific questionnaire-based study by Purcell-Levesque et al.[105] showed a LSD prevalence of 28.9% in 45 male partners from infertile couples. Although the study found no association between attachment related anxiety and low libido, they did find avoidance secondary to female partner's difficulty in reaching orgasms.

Another study by Elia et al.[26] evaluated 156 men of infertile couples using a modified version of the IIEF. Unlike other studies, no correlation was found between LSD and semen parameters; however, none of the patients in the study group were azoospermic.

VALUES

Based on the limited epidemiological evidence of LSD among infertile men, we found that male partners of infertile couples are at higher risk of reporting low desire. According to studies using a validated questionnaire to assess sexual desire, we found that LSD is reported in up to a third of cases. Low desire in infertile men may be more prevalent in azoospermic and severe oligospermic men than other groups of sub fertile men and could be related to hormonal, psychological and interpersonal factors.

REMARKS

Only a few studies looked into the prevalence of LSD in infertile men. Moreover, some studies also looked into SDs in general rather than specifically addressing desire and sometimes the emphasis was on ED. No data are available regarding the management of LSD in infertile patients. Likewise no studies evaluated the effect of hormonal treatment on sexual desire in infertile populations (see above).

CONCLUSIONS

Sexual dysfunctions are frequently reported by male patients of infertile couples, potentially affecting both sexual QoL and reproductive outcomes.

The available evidence suggests that ED may be found in a relatively large proportion of patients affected by couple infertility although prevalence rates differ widely. The evidence suggests that the psychological consequence of MI could significantly affect EF. Indeed, published data confirmed a strong correlation between depressive symptoms and erectile difficulties[5,22,23,40] which may be ascribed both to a feeling of loss of masculinity and to the psychological pressure related to the difficulty to conceive. Moreover, data suggest a positive correlation between the severity of seminal parameters abnormalities and the risk of ED, which could be the consequence of both a higher psychological distress associated to a more severe impairment of reproductive function and to an overall worse health status, which has been largely associated with both MI and ED. Whether ED *per se* could be considered a direct cause of poor reproductive function is currently unknown. However, treating ED appears crucial to ensure an effective sexual relationship aimed to increase both the chance of conceiving and the QoL of the couple. Level 1 data have demonstrated the safety of PDE5is in male patients looking for fatherhood and represent therefore the first line of treatment according to clinical guidelines. Furthermore, infertile patients suffering from ED should be carefully screened for possible metabolic and hormonal abnormalities potentially associated with both conditions. Last, psychological counselling should be considered when the psychogenic factor appears relevant to the EF impairment.

Ejaculatory dysfunctions could be a rare cause of MI. There is consistent evidence from non-randomized studies regarding the efficacy of EEJ and PVS for treating anejaculation in infertile men with neurological diseases. Oral treatment with sympathomimetic and tricyclic antidepressant agents could be of value for the treatment of RE, although larger trials are needed to provide strong data on the efficacy of these drugs. Although ejaculatory dysfunctions account only for a small number of cases of MI, they should be carefully investigated and detected since effective treatments are available.

Furthermore, infertile men should be carefully assessed for PE, which seems to affect a non-negligible rate of patients and deserve to be treated according to clinical guidelines. As for ED, the main reason for PE among infertile men rely on the psychological burden associated with the forced timing of intercourse and the difficulty to conceive. Of clinical relevance, PE may also be associated with prostatitis in some cases,[66] which could be

also a reason for semen impairment. Studies assessing the effect of conventional treatment of PE among infertile men or men of infertile couple are currently lacking.

The psychological distress associated with MI could also lead to LSD. Infertile men or male partners of infertile couples may suffer from low desire with a significant impairment of their sexual activity. Moreover, LSD could be a symptom of systemic conditions, which may also affect fertility.

This systematic review is not devoid of limitations; most of the included studies were retrospective or single-arm studies thus lowering the level of evidence of the reported findings. Moreover, according to our protocol only one database was used for the literature search, thus some eligible studies may have been missed.

Overall, data from this systematic review highlight the importance of discussing also potential sexual issues among patients seeking help for couple infertility.

AKNOWLEDGMENTS

This manuscript was approved by the ESSM executive committee and the ESSM affiliate societies.

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Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

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Conceptualization, P.C. Y.R. and G.C.; Methodology, P.C. G.C..; Investigation, G.R., C.F.J.,A.F.,G.I.R, P.C., J.T.B., A.R.; Writing - Original Draft, G.R., C.F.J.,A.F.,G.I.R, P.C., J.T.B., A.R.; Writing -Review & Editing, G.C., Y.R., M.F., M.M., C. B.; Supervision, G.C., C.B.

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