Chapter 7
Ejaculatory Dysfunction: Retrograde Ejaculation

Jim K. Shen, Salim K. Cheriyan and Edmund Y. Ko

Introduction

Retrograde ejaculation may be defined as a form of ejaculatory dysfunction in which seminal fluid is propelled proximally toward the bladder after leaving the ejaculatory ducts [1]. This process can be complete, in which case no semen is propelled in the antegrade direction, or partial, in which there is still some antegrade propulsion present. Premature ejaculation, anorgasmia, aspermia, lack of emission, and anejaculation accompany retrograde ejaculation as entities within the umbrella of ejaculatory dysfunction [1]. Depending on the series, retrograde ejaculation has been reported to be present in 0.4–2% of cases of male factor infertility [2, 3]. Although uncommon, retrograde ejaculation represents one of the few pathologies within the field of male infertility that, in select cases, can be successfully treated medically.

Clinical Vignette

A 30-year-old man presents to clinic with primary infertility. His wife is 25 years old, healthy, and already has had a child (now 2 years old) with a prior partner. She was evaluated by her reproductive endocrinologist and was found to have no

J.K. Shen (✉) · S.K. Cheriyan · E.Y. Ko
Department of Urology, Loma Linda University Medical Center,
11234 Anderson Street, Room A560, Loma Linda, CA 92354, USA
e-mail: Jishen@llu.edu

S.K. Cheriyan
e-mail: scheriyan@llu.edu

E.Y. Ko
e-mail: eyko@llu.edu

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abnormalities. The couple has been unable to conceive despite sexual intercourse 3–4 times per week. He reports that over the last 2–3 years, the volume of his ejaculate has been decreasing. He denies any other bothersome symptoms. He does not complain of anorgasmia, erectile dysfunction, low sex drive, depression, or fatigue. He does not have hematuria.

His past medical history is notable for type 2 diabetes mellitus diagnosed 6 years ago. He reports no history of prior surgery. His only medication is metformin. There is no family history of note. On physical examination, the patient is obese with a body mass index (BMI) of 38. His secondary sex characteristics appear appropriate. The penis is normal with an orthotopic urethral meatus and no evidence of hypospadias. Both testes are descended and normal in volume with no palpable masses. Both vasa are palpable. Digital rectal examination reveals normal sphincter tone and an appropriately sized prostate. No nodules or cystic structures are palpated. The review of his recent laboratory tests reveals glycosuria and a hemoglobin A1c of 12%. The patient relays that his primary care provider's office staff has contacted him about the laboratory results and he has an upcoming appointment with his primary care physician.

A semen analysis is ordered. The patient returns to clinic 10 days later to review the results. Ejaculate volume is shown to be 0.5 mL, with a sperm concentration of 10 million/mL and a total sperm count of 5 million. Sperm morphology and motility are normal. In accordance with American Society for Reproductive Medicine (ASRM) guidelines, a post-ejaculatory urinalysis is obtained. The results demonstrate >15 million sperm per mL in the collected sample.

The patient is started on oral pseudoephedrine. He tolerates this treatment well and blood pressure remains within normal limits during subsequent follow-up visits. While the patient admits to poor adherence to his metformin regimen in the past, he states that his desire to have a child has motivated him to get his diabetes under control. During the next several weeks, the patient begins to notice increased ejaculate volume. He is advised to continue regular timed sexual intercourse with his wife while on pseudophedrine. Three months later, he returns to clinic with news that his wife has recently become pregnant.

Pathophysiology

Ejaculation is composed of two phases: emission and expulsion. Emission is governed by sympathetic and parasympathetic discharge, which triggers a sequence of events causing seminal fluid to be discharged from the seminal vesicles and prostate. The first step is closure of the bladder neck, an action which is mediated by $\alpha(\text{alpha})_1$ adrenergic receptors. Prostatic secretions followed by seminal vesicle fluid and Cowper's and periurethral gland fluid are subsequently released through the ejaculatory duct and into the prostatic urethra [4].

Expulsion is governed by somatic innervation arising from the S2-4 nerve roots (Fig. 7.1). The motor branch of the pudendal nerve elicits coordinated contraction

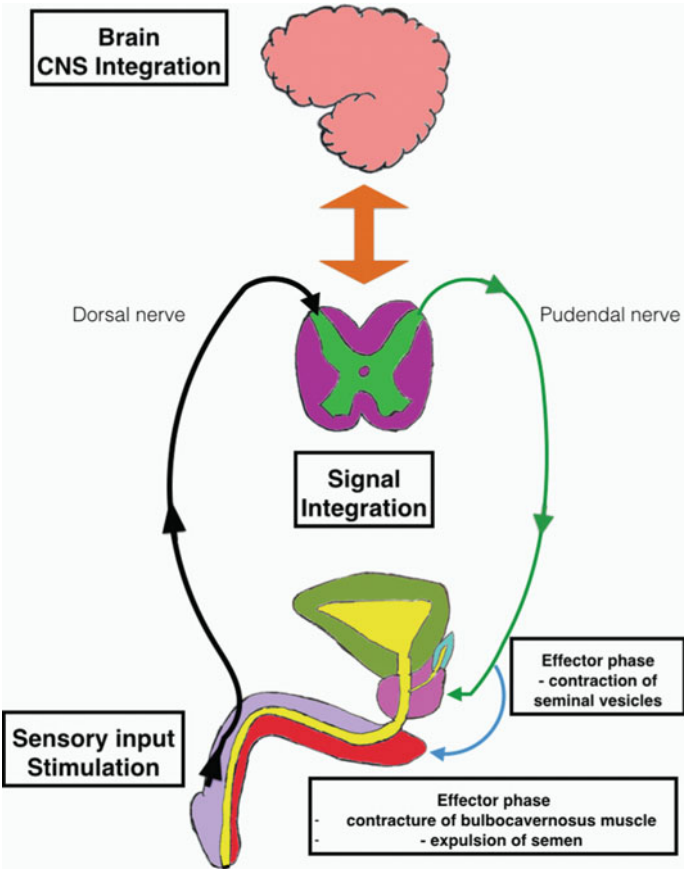

Fig. 7.1 Neural pathways involved in ejaculation

of the bulbocavernosus and bulbospongiosus muscles and nearby pelvic floor muscles. The external urinary sphincter relaxes, permitting antegrade expulsion of seminal fluid. The final factor permitting successful expulsion is the lack of anatomic obstruction.

While retrograde ejaculation is classically attributed to failure of bladder neck coaptation, there has been evidence that this is not the causative process in many cases. A study comparing transrectal color Doppler ultrasonography findings during ejaculation in a healthy man and a spinal cord-injured man demonstrated that in both patients, the bladder neck closed appropriately during ejaculation. However, the external urethral sphincter did not relax sufficiently to allow antegrade flow of semen in the spinal cord-injured man. Once the expulsion phase concluded, the semen in the prostatic urethra slowly flowed retrograde into the bladder [5]. As discussed in further detail in this chapter, α(alpha)-antagonist mediated ejaculatory

dysfunction has been shown to be an anejaculation caused by blockade of $\alpha(\text{alpha})_{1A}$ receptors in the vas deferens, prostate, and seminal vesicles.

In vitro studies have demonstrated that once exposed to the high osmolarity and acidic environment of the urine, spermatozoa lose motility and die quickly [6–8]. These findings underpin the importance of sperm preparation in the sperm retrieval techniques discussed in this chapter.

Diagnosis and Workup

A thorough history and physical examination are crucial to the diagnosis of retrograde ejaculation. Symptoms include decreased ejaculate volume or absent ejaculate as well as cloudy urine. In line with the common causes of retrograde ejaculation, affected men may have comorbidities that can result in neurogenic retrograde ejaculation such as diabetes mellitus or multiple sclerosis or may have had prior surgery that can affect the ability of the bladder neck to coapt. It is important to note that men with isolated retrograde ejaculation still retain the ability to orgasm. As discussed elsewhere in this text, orgasm and ejaculation are separate processes and inability to orgasm does not necessarily cause anejaculation or retrograde ejaculation or vice versa. However, the two may coexist.

Apart from neurologic examination findings associated with comorbidities such as diabetes mellitus or multiple sclerosis, men with isolated retrograde ejaculation tend to have otherwise normal genitourinary examination findings. In some men, the urine may appear cloudy due to the presence of semen. In addition, semen analysis may reveal a low-volume or absent ejaculate with or without oligospermia or azoospermia. In men with these semen analysis findings, obstructive azoospermia remains part of the differential diagnosis. Physical examination therefore represents an important opportunity for the clinician to distinguish between these disease entities. In a man with isolated retrograde ejaculation, both vasa deferentia should be palpable and the digital rectal examination should not reveal any palpable dilated midline structures, which are suggestive of ejaculatory duct obstruction.

The American Society for Reproductive Medicine (ASRM) recommends post-ejaculatory urinalysis for men with ejaculate volume <1.0 mL unless the patient is diagnosed with hypogonadism or congenital bilateral absence of the vas deferens [9]. However, there have been no strict criteria established defining a "normal" versus an "abnormal" post-ejaculatory urinalysis that is suspicious for retrograde ejaculation. Prior investigators have demonstrated the absence of sperm in the pre-ejaculatory urinalysis and the presence of sperm in the urine in post-ejaculatory urinalysis of fertile men. This supports the hypothesis that even in men without retrograde ejaculation, post-ejaculatory urinalyses may contain residual sperm that were washed out from the urethra during micturition [10]. Subsequent efforts have been made to refine the interpretation of post-ejaculatory urinalysis findings. A prospective study comparing 77 men being evaluated for infertility and 71 control male subjects by Mehta et al. showed that although the

presence of sperm in the post-ejaculatory urinalysis was more common in the group being evaluated for infertility, it was still very common even in the control group (98.7% vs. 88.7%, respectively). Subjects who were being evaluated for infertility were more likely to have greater than 50% of their total sperm count in the post-ejaculatory urinalysis and had a higher percentage of their post-ejaculatory urinary sperm count in the initial fraction of voided urine than were control subjects [11]. A similar study of 15 fertile men and 66 non-azoospermic men being evaluated for infertility found that 73% and 65% of the fertile and infertile men, respectively, had sperm in their post-ejaculatory urinalysis. This study did not find a statistically significant difference in proportion of sperm in urine between the two groups [12].

As previous studies demonstrate, there are no physical examination or diagnostic test findings that are pathognomonic for retrograde ejaculation. Findings can overlap considerably between fertile and infertile men. It is important to distinguish retrograde ejaculation from obstructive azoospermia and anejaculation, all three of which may present in a similar manner as azoospermia. Thus, diagnosis relies upon clinical suspicion combined with supportive findings on workup.

Etiologies of Retrograde Ejaculation

Neuropathic Changes

Genitourinary neuropathic diseases such as diabetes mellitus [13] and multiple sclerosis [14] have the potential to cause retrograde ejaculation (Table 7.1). Of these, diabetes mellitus is the most common cause of retrograde ejaculation, with various series reporting prevalence rates of 6–34.6% among diabetic men [15–18]. Of note, these figures may represent an underestimation of the true rate, as retrograde ejaculation among diabetics is felt by some investigators to be

Table 7.1 Etiologies of retrograde ejaculation

Neuropathic	Diabetes mellitus Multiple sclerosis Spinal cord injury
Postsurgical	Transurethral resection of prostate Photovaporization of prostate Transurethral microwave therapy of prostate Transurethral incision of prostate Retroperitoneal lymph node dissection Pelvic/spinal surgery
Medication-induced[a]	Antipsychotics?

[a]α(alpha)-antagonists have been shown to cause anejaculation, not retrograde ejaculation as is widely believed. Antipsychotics may cause ejaculatory dysfunction, but it is not clear whether this represents retrograde or anejaculation

under-diagnosed and underreported [19]. Cases of retrograde ejaculation in this patient population are thought to be caused by an autonomic neuropathy resulting in failure of bladder neck coaptation during ejaculation [20]. As with other sequelae of diabetes mellitus, the presence of ejaculatory dysfunction is correlated with the degree of the particular patient's glycemic control and the duration of diabetes. Theoretically speaking, retrograde ejaculation in patients with multiple sclerosis may be caused by the same mechanism as in diabetic patients, though the authors are not aware of any studies specifically demonstrating this mechanism. Prevalence estimates for retrograde ejaculation specifically are difficult to find in the literature. However, it has been reported that 31–50% of multiple sclerosis patients experience some sort of ejaculatory or orgasmic disturbance [21, 22].

Postsurgical

Postsurgical causes of retrograde ejaculation remain a common cause seen in urologic clinical practice (Table 7.1). Classically, surgical treatment for benign prostatic hypertrophy (BPH) has been long associated with retrograde ejaculation. The other prominent urologic cause of postsurgical retrograde ejaculation is patients undergoing retroperitoneal lymph node dissection (RPLND) for testicular cancer.

Transurethral resection of prostate (TURP) remains the gold standard for the surgical treatment of BPH. A thorough resection leads to a wide-mouthed TUR defect, causing failure of bladder neck coaptation. Patients should be counseled extensively preoperatively that retrograde ejaculation is very common after TURP. A recent review by Marra et al. noted that the overall rate of retrograde ejaculation was 66.1% [23].

Other treatment modalities for BPH have been examined with the goal of achieving comparable clinical efficacy compared to TURP while minimizing the side effects. Photovaporization of the prostate (PVP) was associated with a post-operative rate of retrograde ejaculation of 41.9% in 1 meta-analysis, compared to 61.4% in the TURP group. Less invasive techniques have lower reported rates of retrograde ejaculation. Examples include transurethral needle ablation (TUNA—0%), transurethral microwave therapy (TUMT—21.2%), and transurethral incision of the prostate (TUIP—21.1%) [23]. However, it must be noted that these techniques must be used on appropriately selected patients with smaller prostates.

The prostatic urethral lift procedure (UroLift®, Neotract, Pleasanton, CA) is a promising tissue-sparing technique where intraprostatic implants are delivered to separate the lateral lobes of the prostate without impacting the bladder neck. This offers relief of urinary obstruction without vaporization, ablation, or resection of prostatic tissue. Prospective studies have shown this technique preserves sexual function with no differences in preoperative and postoperative rates of sexual bother or ejaculatory dysfunction. Again, patient selection is important as the UroLift® technique has best results in patients with no median lobe, lack of an elevated bladder neck, and a post void residual of <350 ml [23, 24].

Retroperitoneal lymph node dissection disrupts the pre-aortic postganglionic sympathetic fibers, which can interfere with ejaculation (but not erection) [25]. Classically, reported rates of retrograde ejaculation after bilateral RPLND varied widely, with some series reporting rates of up to 90% [26]. However, recent advances in the understanding of the anatomy and physiology of erection, the adoption of modified unilateral templates of resection (sparing the contralateral sympathetic nerves, and use of nerve-sparing in bilateral templates) have decreased the risk of retrograde ejaculation after RPLND. A more recent series by Beck et al. showed preservation of normal ejaculation in 97% of patients undergoing primary RPLND [27]. Even patients undergoing post-chemotherapy RPLND had antegrade ejaculation rates of up to 85% [28].

Medication Side Effects

α(Alpha)-Antagonists

Alpha-antagonist medications such as tamsulosin, which are widely used for the treatment of lower urinary tract symptoms secondary to benign prostatic enlargement, are well known for their side effect of ejaculatory dysfunction (Table 7.2). Traditional teaching holds that the use of α(alpha)-antagonists causes loss of bladder neck coaptation, resulting in retrograde ejaculation. Over the last decade, multiple studies have demonstrated that this is, in fact, not the cause of α(alpha)-antagonist mediated ejaculatory dysfunction and that this process is actually mediated by antagonism of the $\alpha(\text{alpha})_{1A}$ adrenoreceptor.

Activation of this receptor is required for contraction of the vas deferens [29]. A study involving the use of real-time polymerase chain reaction on radical prostatectomy and cystoprostatectomy specimens showed that $\alpha(\text{alpha})_{1A}$ was also the predominant adrenoreceptor subtype in the seminal vesicles [30], another structure whose function is crucial to the process of ejaculation. The same study also assigned 17 healthy men to treatment with tamsulosin (predominantly $\alpha(\text{alpha})_{1A}$ vs. $\alpha(\text{alpha})_{1D}$ antagonism) and naftopidil (predominantly $\alpha(\text{alpha})_{1D}$ vs. $\alpha(\text{alpha})_{1A}$ antagonism) in a crossover manner. Results demonstrated lack of retrograde ejaculation and lack of sperm in post-ejaculatory urinalysis on transrectal color Doppler ultrasound after administration of either medication [30]. A randomized crossover study of tamsulosin, alfuzosin, and placebo in healthy adult males showed that the use of tamsulosin was associated with a >20% decrease in ejaculate volume in 90% of subjects and anejaculation in 35% of subjects in

Table 7.2 Medications associated with ejaculatory dysfunction

Medication class	Examples
α(alpha)-blockers	Tamsulosin, sildosin, doxazosin, prazosin, terazosin, alfuzosin
Antipsychotics	Levemepromazine, iloperidone, clozapine, risperidone

comparison with alfuzosin and placebo. In this study, there were no statistically significant differences in post-ejaculatory urine sperm concentrations between the three groups [31]. A randomized double-blind crossover study of 15 healthy male urologists demonstrated anejaculation in all subjects after 3 days of silodosin administration, with return of semen volume and sperm count to baseline 3 days after cessation of silodosin [32]. Interestingly, there has been speculation that the presence of ejaculatory dysfunction may serve as a sign of effective treatment of lower urinary tract symptoms in patients taking α(alpha)-antagonists for benign prostatic hyperplasia. In one literature review, an odds ratio of 1.68 was calculated for improvement in International Prostate Symptom Score by 3 points and maximal urinary flow rate by 3 mL per second [33].

Antipsychotic Medications

Antipsychotic medications used for the treatment of psychiatric disorders such as schizophrenia have been associated with rare reports of retrograde ejaculation (Table 7.2). Case reports have implicated several typical and atypical antipsychotics including levomepromazine [34], iloperidone [35], clozapine [36], and risperidone [37–39]—all of which have $\alpha(\text{alpha})_1$-antagonistic effects. The authors are not aware of any studies in which post-ejaculatory urinalyses were collected in patients taking these medications. It is therefore possible, as is the case with reports involving $\alpha(\text{alpha})_1$-antagonists, that these antipsychotics may be causing anejaculation instead of retrograde ejaculation. Alternatively, some investigators have suggested that ejaculatory dysfunction, retrograde or otherwise, may be the indirect result of other endocrine imbalances such as hyperprolactinemia which can be caused by these antipsychotics [40].

Spinal Cord Injury

Retrograde ejaculation has been diagnosed in men with spinal cord injury through the use of penile vibratory stimulation and rectal probe electroejaculation followed by catheterized post-ejaculatory urinalyses [41–43]. Certainly, there are known ejaculatory derangements that other investigators have proposed to be the cause of retrograde ejaculation in men with spinal cord injury. These include the tendency for sacral cord injuries to result in loss of the expulsion phase of ejaculation as well as detrusor-sphincter and detrusor-bladder neck dyssynergia [44–46]. However, as noted previously, post-ejaculatory urinalyses containing sperm are found even in neurologically intact men. Studies clearly demonstrating a mechanism of retrograde ejaculation in spinal cord-injured men remain relatively rare, with a notable exception being a study of nine men undergoing penile vibratory stimulation or electroejaculation with simultaneous urodynamic catheter monitoring of internal

and external urethral sphincter pressures. This study demonstrated that in each of the nine men, forceful contraction of the external followed by the internal urethral sphincter preceded ejaculation, but that in the men undergoing electroejaculation, the external sphincter pressure exceeded that of the internal sphincter shortly after ejaculation, providing a possible mechanism for electroejaculation-induced retrograde ejaculation [47]. As mentioned earlier, transrectal color Doppler ultrasonography studies have shown that the bladder neck or internal sphincter closes appropriately during ejaculation in some patients with spinal cord injury. Rather, it is a failure of external urethral sphincter relaxation, or a form of detrusor-sphincter dyssynergia, that causes retrograde ejaculation in these patients [5]. While rare, spinal cord conditions such as perineural cysts or tethered cord syndrome can cause retrograde ejaculation as well [48, 49].

Treatment of Retrograde Ejaculation

Noninvasive Techniques

The method of treatment of retrograde ejaculation can vary widely depending on severity and etiology (Table 7.3). In general, less invasive treatment options are preferred for initial management. In some cases simple substitution, discontinuation, or dose reduction of the offending medication can restore normal ejaculation. In cases of retrograde ejaculation caused by antipsychotic medication, referral to a psychiatrist for dosage adjustment or substitution with a different medication may be indicated. Dose reduction has been reported to be successful in restoring normal ejaculation in patients taking risperidone, for example [38]. Prior authors have reported on circumvention of retrograde ejaculation by instructing men to ejaculate with a full bladder. According to one published case report, two patients with retrograde ejaculation were able to convert to antegrade ejaculation with the use of this technique [7]. In a separate report, ejaculate retrieved in this manner from one

Table 7.3 Treatment of retrograde ejaculation

Noninvasive	Discontinuation, dose reduction of medications	Ejaculation with full bladder	
Medical	α(alpha)-agonists (midodrine, pseudophedrine, ephedrine)	Anticholinergics, antihistamines, tricyclic antidepressants	
Sperm retrieval	Modified Hotchkiss technique	Retrograde instillation of sperm media and extraction	Epididymal or testicular sperm extraction
Surgical	Young-Dees technique (bladder neck reconstruction)	Y-V plasty of bladder neck	Transurethral collagen injection of bladder neck

patient was used for intrauterine insemination and resulted in a successful pregnancy [50]. Other noninvasive techniques include the combination of urinary alkalinization followed by voiding of urine directly into the vagina after intercourse or intravaginal insemination of the postcoital urine–semen mixture using a syringe [51–53].

Medical Therapy

Medical therapy has been described in the literature, mostly in the form of α(alpha)-agonists, tricyclic antidepressants, and antihistamines aimed at increasing sympathetic tone and/or decreasing the parasympathetic tone of the bladder neck. Commonly used α(alpha)-agonists include midodrine (known as milodrin in several older studies), pseudoephedrine, and ephedrine. The use of these medications has been described in the past [54, 55]. A few notable recent studies involving patients diagnosed with retrograde ejaculation have been published. A study of 33 patients with diabetes mellitus and retrograde ejaculation found that imipramine, pseudoephedrine, and a combination of both were able to produce antegrade ejaculation in 38.5, 47.8, and 61.5% of cases, respectively [56]. Hsiao et al. were able to restore antegrade ejaculation using pseudoephedrine in two of four patients with retrograde ejaculation after chemotherapy and retroperitoneal lymph node dissection for testicular cancer [57]. Tomasi et al. reported on the use of intramuscular self-injection of methoxamine 30 min prior to sexual intercourse or masturbation in two patients. Antegrade ejaculation was restored in both patients with one of the two patients able to achieve pregnancy after 3 months of methoxamine treatment [58].

Tricyclic antidepressants also have been used for the medical treatment of retrograde ejaculation. In one series, 11 of 11 patients with retrograde ejaculation after retroperitoneal surgery were treated with daily imipramine for 7 days prior to the female partner's planned ovulation. Using this regimen, antegrade ejaculation was produced in all 11 patients with only minor side effects such as dizziness, weakness, nausea, or sweating. Two spontaneous pregnancies were reported and two successful fertilizations without successful pregnancy were induced with the help of intracytoplasmic sperm injection (ICSI) [59]. In another study, antegrade ejaculation was achieved in three of seven patients using imipramine. Of these three patients, two went on to conceive naturally. All three of these patients initially had partial retrograde ejaculation [2]. The use of various other medications has been described in some older studies including the antihistamines bromphenoramine [60] and chlorpheniramine—the latter in combination with phenylpropanalamine [55].

A meta-analysis reported that of retrograde ejaculation patients treated with medical therapy, antegrade ejaculation was achieved in 50% and spontaneous pregnancy was achieved in 34%. The authors found that imipramine was the most widely used medication but did note that there were no randomized controlled trials comparing the various medical treatments of retrograde ejaculation on a head-to-head basis [55]. Indeed, some clinicians prefer the use of alpha-agonists

such as pseudoephedrine due to the potentially more dangerous adverse effects associated with imipramine [57].

Sperm Retrieval

In cases of retrograde ejaculation that persist despite the aforementioned interventions, sperm retrieval therapy may be used. Sperm retrieval may also be accomplished by a multistep process known as the modified Hotchkiss technique. The initial step involves the use of agents to make the urine osmolality and pH more favorable to sperm motility and viability. Some investigators have accomplished this by first asking the patient to empty his bladder and then catheterizing the bladder and instilling an alkalinizing medium. Others have favored the use of oral sodium bicarbonate and hydration. The patient is then asked to empty his bladder prior to any ejaculation attempts. Masturbation or, if necessary, penile vibratory stimulation or electroejaculation is then used to produce retrograde ejaculation into the previously instilled medium or the alkalinized urine. The sperm are retrieved either by voiding or bladder catheterization. The urine is centrifuged and the sperm pellet is resuspended in a buffered medium. The suspension is then used for intravaginal insemination or assisted reproductive techniques such as intrauterine insemination, in vitro fertilization, and ICSI. Many variations on this technique have been described, ranging from the use of unprepared urine and sperm to centrifugation and suspension of the sperm within media such as Ham's F-10 medium, bovine serum albumin, human serum albumin, and phosphate buffered solution [2, 51, 61–64]. Prior investigators who have reported successful pregnancies with sperm retrieval were able to alkalinize the urine to a "physiological" pH of 7.2 [65].

Generally, this process is timed in accordance with the partner's luteinizing hormone (LH) surge in order to maximize the probability of success. However, there are at least two published reports of successful pregnancy or live birth via ICSI using thawed sperm that were initially retrieved by a modified Hotchkiss technique and then cryopreserved for a period of time [66, 67]. One recent review of 15 published articles using modified Hotchkiss techniques dating back to the 1970s calculated a pregnancy rate of 15% per cycle [68].

Surgical Therapy

Surgical correction of retrograde ejaculation has been described sparingly in the literature, though with a high rate of success in the limited number of cases reported. The Young-Dees technique of bladder neck reconstruction, which has been used for the management of incompetent bladder necks due to trauma, neurogenic bladder, and exstrophy, has also been applied to patients with retrograde

ejaculation. One series reported the successful conversion of retrograde into antegrade ejaculation in four of five patients [69]. Using a similar technique, Ramadan et al. described the use of trigonal urothelium and musculature in order to reconstruct the proximal urethra and bladder neck around a 12-French catheter. This technique was used in five men with retrograde ejaculation after bladder neck surgery for bilharzial obstruction, also with restoration of antegrade ejaculation in four of the five men [70]. A third publication reported successful correction of retrograde ejaculation in two men who developed retrograde ejaculation after Y-V plasty of the bladder neck. Normal ejaculation was achieved in both patients and one patient was able to produce a successful pregnancy [71].

A less invasive option in the form of transurethral collagen injection of the bladder neck has been used for the treatment of retrograde ejaculation. A prospective trial of 23 patients with type 1 diabetes mellitus randomized to transurethral collagen injection of the bladder neck or a sham surgery demonstrated statistically significant improvements in antegrade ejaculate volume, sperm count, motility, and progressive motility in the treatment group at 1 year postoperatively. There were no complications reported and no significant differences in erectile function as measured by International Index of Erectile Function-5 questionnaire scores. Interestingly, the patients undergoing collagen injection demonstrated improvements in depression and anxiety as measured by validated questionnaires [72]. A case report from Japan demonstrated the use of this technique in a 40-year-old male with retrograde ejaculation following thoracic spinal cord injury. Preoperatively, his retrograde ejaculation was documented by transrectal Doppler ultrasound. He then underwent transurethral collagen injection of his bladder neck. At 14 days postoperatively, repeat ultrasound demonstrated the conversion of his retrograde ejaculation to antegrade ejaculation. The therapeutic effect of the collagen had disappeared at 1 year postoperatively, but the injection was repeated, again with successful restoration of antegrade ejaculation [73]. A similar outcome was observed following bladder neck collagen injection in a 36-year-old man who presented with primary infertility refractory to pseudoephedrine therapy. He had had a history of Y-V plasty of the bladder neck, a surgical method of bladder neck obstruction in which a Y-shaped incision is made through the area of obstruction and the apex of the V flap is sutured to the Y incision. Successful pregnancy was achieved with intrauterine insemination 3 weeks postoperatively [74]. In these reported cases, the surgery seems to have been well tolerated. That said, due to their invasiveness and the risk of postoperative complications, the authors recommend that surgery should be considered as a last resort for the treatment of retrograde ejaculation.

When successful, the techniques discussed above merely make the patient's own sperm available for insemination but do not improve the quality of the sperm. Thus, in patients who produce poor quality sperm, these techniques may need to be bypassed and assisted reproductive techniques may be indicated. Case reports and case series describe the use of vasal aspiration and intrauterine insemination [75],

percutaneous epididymal sperm aspiration [76], and testicular sperm extraction and ICSI [57, 77] in patients with retrograde ejaculation, resulting in successful pregnancy.

Conclusion

Recent evidence suggests that some classical examples of retrograde ejaculation are in fact more appropriately categorized as examples of anejaculation. Furthermore, in many cases appropriately labeled as retrograde ejaculation, alternative causative mechanisms besides failure of bladder neck closure may be at fault. More so than certain other forms of male infertility, retrograde ejaculation represents an entity that can be successfully treated. Thus, these are important findings that deserve further study and may impact treatment options in the future. For patients with otherwise healthy sperm, as long as the proper neurologic and anatomic derangements are identified and effective treatment strategies can be implemented, successful conception should be within reach.

References

1. Sigman M. Introduction: ejaculatory problems and male infertility. Fertil Steril. 2015;104(5):1049–50.
2. Okada H, Fujioka H, Tatsumi N, Kanzaki M, Inaba Y, Fujisawa M, et al. Treatment of patients with retrograde ejaculation in the era of modern assisted reproduction technology. J Urol. 1998;159(3):848–50.
3. Yavetz H, Yogev L, Hauser R, Lessing JB, Paz G, Homonnai ZT. Retrograde ejaculation. Hum Reprod. 1994;9(3):381–6.
4. Alwaal A, Breyer BN, Lue TF. Normal male sexual function: emphasis on orgasm and ejaculation. Fertil Steril. 2015;104(5):1051–60.
5. Nagai A, Watanabe M, Nasu Y, Iguchi H, Kusumi N, Kumon H. Analysis of human ejaculation using color doppler ultrasonography: a comparison between antegrade and retrograde ejaculation. Urology. 2005;65(2):365–8.
6. Aust TR, Brookes S, Troup SA, Fraser WD, Lewis-Jones DI. Development and in vitro testing of a new method of urine preparation for retrograde ejaculation; the Liverpool solution. Fertil Steril. 2008;89(4):885–91.
7. Crich JP, Jequier AM. Infertility in men with retrograde ejaculation: the action of urine on sperm motility, and a simple method for achieving antegrade ejaculation. Fertil Steril. 1978;30(5):572–6.
8. Makler A, David R, Blumenfeld Z, Better OS. Factors affecting sperm motility. Vii. Sperm viability as affected by change of ph and osmolarity of semen and urine specimens. Fertil Steril. 1981;36(4):507–11.
9. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2015;103(3):e18–25.
10. Engelbertz F, Korda JB, Engelmann U, Rothschild M, Banaschak S. Longevity of spermatozoa in the post-ejaculatory urine of fertile men. Forensic Sci Int. 2010;194(1–3):15–9.

11. Mehta A, Jarow JP, Maples P, Sigman M. Defining the "normal" postejaculate urinalysis. J Androl. 2012 Sep-Oct;33(5):917–20.
12. Sigman M, Boyle K, Jarow JP. Prevalence of sperm in the post-ejaculatory urine of fertile and subfertile men. Urology. 2008;71(1):110–2.
13. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care. 2003;26(5):1553–79.
14. Wei DY, Drake MJ. Undiagnosed neurological disease as a potential cause of male lower urinary tract symptoms. Curr Opin Urol. 2016;26(1):11–6.
15. Dinulovic D, Radonjic G. Diabetes mellitus/male infertility. Arch Androl. 1990;25(3):277–93.
16. Fedder J, Kaspersen MD, Brandslund I, Hojgaard A. Retrograde ejaculation and sexual dysfunction in men with diabetes mellitus: a prospective, controlled study. Andrology. 2013;1(4):602–6.
17. Delfino M, Imbrogno N, Elia J, Capogreco F, Mazzilli F. Prevalence of diabetes mellitus in male partners of infertile couples. Minerva urologica e nefrologica Ital J Urol Nephrol. 2007;59(2):131–5.
18. Mulholland J, Mallidis C, Agbaje I, McClure N. Male diabetes mellitus and assisted reproduction treatment outcome. Reprod Biomed Online. 2011;22(2):215–9.
19. Sexton WJ, Jarow JP. Effect of diabetes mellitus upon male reproductive function. Urology. 1997;49(4):508–13.
20. Gaunay G, Nagler HM, Stember DS. Reproductive sequelae of diabetes in male patients. Endocrinol Metab Clin North Am. 2013;42(4):899–914.
21. Hennessey A, Robertson NP, Swingler R, Compston DA. Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. J Neurol. 1999;246(11):1027–32.
22. Zorzon M, Zivadinov R, Bosco A, Bragadin LM, Moretti R, Bonfigli L, et al. Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. Multiple Sclerosis. 1999;5(6):418–27.
23. Marra G, Sturch P, Oderda M, Tabatabaei S, Muir G, Gontero P. Systematic review of lower urinary tract symptoms/benign prostatic hyperplasia surgical treatments on men's ejaculatory function: time for a bespoke approach? Int J Urol (Official Journal of the Japanese Urological Association). 2016;23(1):22–35.
24. Woo HH, Bolton DM, Laborde E, Jack G, Chin PT, Rashid P, et al. Preservation of sexual function with the prostatic urethral lift: a novel treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Sex Med. 2012;9(2):568–75.
25. Baniel J, Sella A. Complications of retroperitoneal lymph node dissection in testicular cancer: primary and post-chemotherapy. Semin Surg Oncol. 1999;17(4):263–7.
26. Pearce S, Steinberg Z, Eggener S. Critical evaluation of modified templates and current trends in retroperitoneal lymph node dissection. Current Urol Reports. 2013;14(5):511–7.
27. Beck SD, Bey AL, Bihrle R, Foster RS. Ejaculatory status and fertility rates after primary retroperitoneal lymph node dissection. J Urol. 2010;184(5):2078–80.
28. Masterson TA, Cary C, Rice KR, Foster RS. The evolution and technique of nerve-sparing retroperitoneal lymphadenectomy. Urol Clin North Am. 2015;42(3):311–20.
29. Sanbe A, Tanaka Y, Fujiwara Y, Tsumura H, Yamauchi J, Cotecchia S, et al. Alpha1-adrenoceptors are required for normal male sexual function. Br J Pharmacol. 2007;152(3):332–40.
30. Hisasue S, Furuya R, Itoh N, Kobayashi K, Furuya S, Tsukamoto T. Ejaculatory disorder caused by alpha-1 adrenoceptor antagonists is not retrograde ejaculation but a loss of seminal emission. Int J Urol (Official Journal of the Japanese Urological Association). 2006;13(10):1311–6.
31. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. J Urol. 2006;176(4 Pt 1):1529–33.
32. Kobayashi K, Masumori N, Hisasue S, Kato R, Hashimoto K, Itoh N, et al. Inhibition of seminal emission is the main cause of anejaculation induced by a new highly selective alpha1a-blocker in normal volunteers. J Sex Med. 2008;5(9):2185–90.

33. Kaplan SA. Side effects of alpha-blocker use: retrograde ejaculation. Rev Urol. 2009 Fall;11 (Suppl 1):S14–8.
34. Mizoguchi Y. Levomepromazine-induced retrograde ejaculation. J Neuropsychiatry Clin Neurosci. 2012 Winter;24(1):E32.
35. Freeman SA. Iloperidone-induced retrograde ejaculation. Int Clin Psychopharmacol. 2013;28 (3):156.
36. Jeffries JJ, Vanderhaeghe L, Remington GJ, Al-Jeshi A. Clozapine-associated retrograde ejaculation. Can J Psychiatry Revue canadienne de psychiatrie. 1996;41(1):62–3.
37. Kandasamy A. Paliperidone as an alternative for risperidone in a case of schizophrenia with retrograde ejaculation. J Neuropsychiatry Clin Neurosci. 2012 Summer;24(3):E17–8.
38. Loh C, Leckband SG, Meyer JM, Turner E. Risperidone-induced retrograde ejaculation: case report and review of the literature. Int Clin Psychopharmacol. 2004;19(2):111–2.
39. Shiloh R, Weizman A, Weizer N, Dorfman-Etrog P, Munitz H. Risperidone-induced retrograde ejaculation. Am J Psychiatry. 2001;158(4):650.
40. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs. 2014;28 (5):421–53.
41. Brackett NL, Ferrell SM, Aballa TC, Amador MJ, Padron OF, Sonksen J, et al. An analysis of 653 trials of penile vibratory stimulation in men with spinal cord injury. J Urol. 1998;159 (6):1931–4.
42. McGuire C, Manecksha RP, Sheils P, McDermott TE, Grainger R, Flynn R. Electroejaculatory stimulation for male infertility secondary to spinal cord injury: the Irish experience in national rehabilitation hospital. Urology. 2011;77(1):83–7.
43. Heruti RJ, Katz H, Menashe Y, Weissenberg R, Raviv G, Madjar I, et al. Treatment of male infertility due to spinal cord injury using rectal probe electroejaculation: the Israeli experience. Spinal Cord. 2001;39(3):168–75.
44. Brindley GS. Reflex ejaculation under vibratory stimulation in paraplegic men. Paraplegia. 1981;19(5):299–302.
45. Schurch B, Yasuda K, Rossier AB. Detrusor bladder neck dyssynergia revisited. J Urol. 1994;152(6 Pt 1):2066–70.
46. Soler JM, Previnaire JG. Ejaculatory dysfunction in spinal cord injury men is suggestive of dyssynergic ejaculation. Eur J Phys Rehabil Med. 2011;47(4):677–81.
47. Sonksen J, Ohl DA, Wedemeyer G. Sphincteric events during penile vibratory ejaculation and electroejaculation in men with spinal cord injuries. J Urol. 2001;165(2):426–9.
48. Shibahara H, Toji H, Shigeta M, Yoshimoto T, Shima H, Koyama K. Successful pregnancies in a case of retrograde ejaculation associated with tethered spinal cord syndrome. J Assist Reprod Genet. 2000;17(4):233–7.
49. Singh PK, Singh VK, Azam A, Gupta S. Tarlov cyst and infertility. J Spinal Cord Med. 2009;32(2):191–7.
50. Templeton A, Mortimer D. Successful circumvention of retrograde ejaculation in an infertile diabetic man. Case report. Br J Obstet Gynaecol. 1982;89(12):1064–5.
51. Leiva R. Retrograde ejaculation: simpler treatment. Fertil Steril. 2007 Jul;88(1):212 e213–4.
52. Marmar JL, Praiss DE, DeBenedictis TJ. Postcoital-voiding insemination: technique for patients with retrograde ejaculation and infertility. Urology. 1977;9(3):288–90.
53. Cleine JH. Retrograde ejaculation: can sperm retrieval be simpler and noninvasive? Fertil Steril. 2000;74(2):416–7.
54. Gilja I, Parazajder J, Radej M, Cvitkovic P, Kovacic M. Retrograde ejaculation and loss of emission: possibilities of conservative treatment. Eur Urol. 1994;25(3):226–8.
55. Kamischke A, Nieschlag E. Update on medical treatment of ejaculatory disorders. Int J Androl. 2002;25(6):333–44.

56. Arafa M, El Tabie O. Medical treatment of retrograde ejaculation in diabetic patients: a hope for spontaneous pregnancy. J Sex Med. 2008;5(1):194–8.
57. Hsiao W, Deveci S, Mulhall JP. Outcomes of the management of post-chemotherapy retroperitoneal lymph node dissection-associated anejaculation. BJU Int. 2012;110(8):1196–200.
58. Tomasi PA, Fanciulli G, Delitala G. Successful treatment of retrograde ejaculation with the alpha1-adrenergic agonist methoxamine: Case study. Int J Impot Res. 2005 May-Jun;17 (3):297–299..
59. Ochsenkuhn R, Kamischke A, Nieschlag E. Imipramine for successful treatment of retrograde ejaculation caused by retroperitoneal surgery. Int J Androl. 1999;22(3):173–7.
60. Andaloro VA Jr, Dube A. Treatment of retrograde ejaculation with brompheniramine. Urology. 1975;5(4):520–2.
61. Nikolettos N, Al-Hasani S, Baukloh V, Schopper B, Demirel LC, Baban N, et al. The outcome of intracytoplasmic sperm injection in patients with retrograde ejaculation. Hum Reprod. 1999;14(9):2293–6.
62. Saito K, Kinoshita Y, Yumura Y, Iwasaki A, Hosaka M. Successful pregnancy with sperm retrieved from the bladder after the introduction of a low-electrolyte solution for retrograde ejaculation. Fertil Steril. 1998;69(6):1149–51.
63. Scammell GE, Stedronska-Clark J, Edmonds DK, Hendry WF. Retrograde ejaculation: Successful treatment with artificial insemination. Br J Urol. 1989;63(2):198–201.
64. Zhao Y, Garcia J, Jarow JP, Wallach EE. Successful management of infertility due to retrograde ejaculation using assisted reproductive technologies: a report of two cases. Arch Androl. 2004 Nov-Dec;50(6):391–394..
65. Scammell GE. Successful treatment of infertility due to retrograde ejaculation. J R Soc Med. 1981;74(12):926–7.
66. Philippon M, Karsenty G, Bernuz B, Courbiere B, Brue T, Saias-Magnan J, et al. Successful pregnancies and healthy live births using frozen-thawed sperm retrieved by a new modified hotchkiss procedure in males with retrograde ejaculation: first case series. Basic Clin Androl. 2015;25:5.
67. Jimenez C, Grizard G, Pouly JL, Boucher D. Birth after combination of cryopreservation of sperm recovered from urine and intracytoplasmic sperm injection in a case of complete retrograde ejaculation. Fertil Steril. 1997;68(3):542–4.
68. Jefferys A, Siassakos D, Wardle P. The management of retrograde ejaculation: a systematic review and update. Fertil Steril. 2012;97(2):306–12.
69. Middleton RG, Urry RL. The young-dees operation for the correction of retrograde ejaculation. J Urol. 1986;136(6):1208–9.
70. Ramadan AE, el-Demiry MI, Ramadan AE. Surgical correction of post-operative retrograde ejaculation. Br J Urol. 1985 Aug;57(4):458–61.
71. Abrahams JI, Solish GI, Boorjian P, Waterhouse RK. The surgical correction of retrograde ejaculation. J Urol. 1975;114(6):888–90.
72. Kurbatov D, Russo GI, Galstyan GR, Rozhivanov R, Lepetukhin A, Dubsky S, et al. Correction of retrograde ejaculation in patients with diabetes mellitus using endourethral collagen injection: preliminary results. J Sex Med. 2015;12(11):2126–9.
73. Nagai A, Nasu Y, Watanabe M, Tsugawa M, Iguchi H, Kumon H. Analysis of retrograde ejaculation using color doppler ultrasonography before and after transurethral collagen injection. Int J Impot Res. 2004;16(5):456–8.
74. Reynolds JC, McCall A, Kim ED, Lipshultz LI. Bladder neck collagen injection restores antegrade ejaculation after bladder neck surgery. J Urol. 1998;159(4):1303.
75. Belker AM, Sherins RJ, Bustillo M, Calvo L. Pregnancy with microsurgical vas sperm aspiration from a patient with neurologic ejaculatory dysfunction. J Androl. 1994 Nov-Dec;15 Suppl:6S-9S.

76. Tsirigotis M, Pelekanos M, Beski S, Gregorakis S, Foster C, Craft IL. Cumulative experience of percutaneous epididymal sperm aspiration (pesa) with intracytoplasmic sperm injection. J Assist Reprod Genet. 1996;13(4):315–9.
77. Rosenlund B, Sjoblom P, Tornblom M, Hultling C, Hillensjo T. In-vitro fertilization and intracytoplasmic sperm injection in the treatment of infertility after testicular cancer. Hum Reprod. 1998;13(2):414–8.