Reproductive Health of Men with Spinal Cord Injury

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Most men with spinal cord injury (SCI) are infertile due to a combination of erectile dysfunction, ejaculatory dysfunction, and abnormal semen quality. This article addresses issues that should be considered when managing the reproductive health of men with SCI. The authors present recommendations based on their decades of experience in managing the reproductive health of more than 1,000 men with SCI. Men with SCI face obstacles when pursuing sexual activity and/or biologic fatherhood. Hypogonadism and premature symptoms of aging may interfere with sexual function. Erectile dysfunction is prevalent in the SCI population, and treatments for erectile dysfunction in the general population are also effective in the SCI population. Most men with SCI cannot ejaculate with sexual intercourse. The procedures of penile vibratory stimulation (PVS) and/or electroejaculation (EEJ) are effective in obtaining an ejaculate from 97% of men with SCI. The ejaculate often contains sufficient total motile sperm to consider the assisted conception procedures of intrauterine insemination or even intravaginal insemination at home. If PVS and/or EEJ fail, sperm may be retrieved surgically from the testis or epididymis. Surgical sperm retrieval typically yields enough motile sperm only for in vitro fertilization with intracytoplasmic sperm injection. The majority of new cases of SCI occur in young men at the peak of their reproductive health. With proper medical management, these men can expect to experience active sexual lives and biologic fatherhood, if these are their goals. Numerous tools are available to physicians for helping these patients reach their goals. **Key words:** *ejaculation, electroejaculation, erection, fertility, infertility, penile vibratory stimulation, semen, sperm, spinal cord injuries*

Introduction

Spinal cord injury (SCI) most commonly affects men at the peak of their reproductive health.¹ Following SCI, most men experience impairments in sexual function and fertility. This article addresses conditions that should be taken into account when managing the reproductive health of men with SCI.

Men with SCI Are at Higher Risk for Hypogonadism

Testosterone is important for sexual function, particularly libido, erection ability, ejaculatory function, spermatogenesis, and mood. Hypogonadism puts men at risk for sexual dysfunction and infertility, cardiovascular-related events, and fracture from osteoporosis²; men with SCI are already at risk for these conditions. Low testosterone is observed in 39% to 46% of men

with SCI, and it is related to increased fat mass and duration of severity of injury.^{3,4} Although testosterone levels naturally decline in aging men, the age-related decline in circulating total testosterone concentration is greater in men with SCI. Compared with the general population, men with SCI have low serum total testosterone concentration earlier in life and at a higher prevalence by decade of life. Low testosterone can also occur within the first year of injury as a result of dysfunction of the hypothalamic-pituitary-gonadal axis secondary to SCI.³

Other causes of low testosterone found in the general population, including head injury, obesity, diabetes, metabolic syndrome, and hyperlipidemia,² can also contribute to low testosterone in men with SCI because they are prone to these comorbidities. Persons with sleep apnea or disordered breathing (almost 60% in persons with complete quadriplegia)⁵ are also at risk for low testosterone. Replacing serum

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testosterone levels to eugonadal levels with proper monitoring² is of benefit to men with chronic SCI in terms of improved sexual drive, erection function, energy, mood, muscle strength, and body composition. Forms of gonadotropin stimulation can be used in men who want to have children. In younger hypogonadal men with SCI (33-49 years of age), the improvements in lean tissue mass and resting energy expenditure are retained even up to 6 months after cessation of testosterone replacement therapy.³

Aging

During the first year after acute injury, there is a dramatic loss of sublesional lean tissue mass. Maintenance of favorable body composition is difficult because of an inability to engage in normal levels of physical activity.³ Adverse metabolic consequences associated with lower levels of activity then worsen with age. Metabolic changes, especially dyslipidemia, negatively affect erectile function. Changes to physical appearance after SCI can affect sexual self-esteem. Sacropenia, declining shoulder and arm strength, and cumulative trauma resulting in arthritis can affect sexual positioning. SCI and aging itself make men with SCI more susceptible to stroke. Becoming less symptomatic to autonomic dysreflexia (AD) over the years does not guarantee a lower, safer blood pressure with sexual activity.⁶

Other issues with aging that may interfere with sexuality for men with SCI include increased risk for bladder and renal issues, potentially worsening incontinence (associated with age in the general population), benign prostatic hypertrophy affecting voiding, prostate surgeries affecting erectile ability and continence, and neurogenic bowel incontinence. Chronic hypotension in persons with SCI is associated with deficits in memory and possibly attention and processing speed.⁷ There is some evidence that having an SCI is associated with a subsequent increased risk of Parkinson's disease and dementia.⁸

Fertility

Following SCI, the majority of men cannot father biologic children naturally and require medical interventions. There are 3 common sequelae of

SCI that impact fertility: erectile dysfunction, ejaculatory dysfunction, and abnormal semen quality.⁹ Techniques to help achieve improved erections and ejaculation, coupled with advances in assisted reproductive technologies, have made fathering biologic children a reality for men living with SCI.

Erectile dysfunction

Normal penile innervation requires an intact autonomic nervous system, both sympathetic and parasympathetic, as well as functional somatic innervation for sensory and motor inputs. The 2 types of erections are reflexogenic and psychogenic. Reflexogenic erections necessitate an intact sacral reflex arc via the S2-S4 nerve roots. This arc is usually maintained in injuries rostral to L2. In contrast, psychogenic erections are generated by thoughts and erotic stimuli and are independent of direct genital stimulation. These stimuli are responsible for maintaining the erection during intercourse. Psychogenic erections require intact thoracolumbar roots and the supraspinal input to the cord at that level, and therefore they are often lost with injuries to the thoracic spinal cord.¹⁰ As a consequence, some men with SCI are capable of initiating reflexogenic erections, but they cannot maintain them due to a loss of psychogenic erections.¹¹ It is possible that a select lesion to the spinal cord just below the thoracolumbar output, but above S2, could preserve both psychogenic and reflexogenic erections.

If the basic mechanisms for erection (normal vasculature and an intact sacral reflex arc) are preserved in men with SCI, they may benefit from treatments for erectile dysfunction that are also used in the general population. The most common treatment for erectile dysfunction is the oral administration of phosphodiesterase type 5 inhibitors (PDE-5i). PDE-5i prevent the degradation of cyclic GMP (cGMP) by PDE-5. Once an erection is initiated, cGMP maintains vascular smooth muscle relaxation, which is critical for the maintenance of erection. Hence, PDE-5i cannot initiate erections but instead it maintains erections.¹²

The use of PDE-5i has been successful in men with SCI (>80% response), especially in those

with an upper motor lesion.^{12,13} Headache and facial flushing are common side effects and can be misinterpreted as AD and erroneously treated with nitrates, which is contraindicated. PDE-5i rely on nitric oxide (NO) to relax the smooth muscle in erectile tissue and create an erection. NO, which is usually released from nerve endings secondary to sexual arousal, can be released by sacral reflex activity in men with higher and/or complete SCI. NO is also produced by healthy endothelium. Men with sacral lesions likely have less NO release, which makes them less responsive to the PDE-5i and even to intracavernosal injection. Furthermore, PDE-5i require testosterone for their action; men with SCI who fail PDE-5i should be assessed for hypogonadism and treated for that condition if found.

PDE-5i are very safe medications. However, they can cause hypotension and dizziness in men with SCI. To avoid symptomatic hypotension, it is prudent to start with lower doses of as-needed sildenafil (Viagra) and vardenafil (Levitra), whose maximal effect is from 1 to 4 hours after administration. The use of tadalafil (Cialis as needed or Cialis once a day) can also be beneficial, but it has a longer acting effect. Daily low dose use in persons with quadriplegia may cause frequent unwanted erections. A new PDE5i, avanafil (Stendra), is available in the United States but has not been evaluated in the spinal cord population. PDE-5i have also been shown to have a slight positive influence on ejaculatory rates (19% on vardenafil compared to 10% on placebo) in men with SCI.¹⁴

Second-line options for erection enhancement include the use of vacuum devices (a cylinder is placed over the penis and blood is drawn into the tissues) to create an erection that is maintained by a penile ring at the base or the use of penile rings to maintain a natural erection. The penile ring should not be left on for more than 45 minutes; this can be a potential hazard in men who are genitally insensate and would not feel pain. Third-line choices include the use of direct medications through injection or intraurethral application. The more invasive intracavernosal (penile) injections of single or mixed medications (prostaglandin E1, papaverine, and phentolamine) that directly relax the cavernosal smooth muscle are very

effective, but there is the risk of priapism in the SCI population. Very small doses and appropriate training are required, along with instructions on how to conservatively reduce the erection with the use of over-the-counter sympathomimetic medications such as pseudoephedrine (with awareness of AD risk), ejaculation (if possible), or the application of cold to the penis. Prevention is the best strategy. The intraurethral application of prostaglandin (MUSE) has not been that successful in the SCI population.¹⁵

The fourth-line treatment is surgical penile prosthesis surgery. This is only utilized when reversible methods are not satisfactory or fail or there are other bladder management issues for which an internal phallic prosthesis may be helpful.¹⁶ Other considerations include perineal training in patients with a preserved sacral segment, and surgical options such as a Brindley sacral anterior root stimulator after sacral dorsal rhizotomy or a definitive sacral neuromodulation implant.¹⁵

Ejaculatory dysfunction

Normal ejaculation requires integration in the activity of the spinal cord segments T10-L2 and S2-S4 as well as the supraspinal input (stimulatory and inhibitory) to those cord segments. Emission of semen into the urethra and simultaneous closure of the bladder neck requires sympathetic innervation from T10-L2. S2-S4 directs motor innervation of the penis, projectile ejaculation of semen, and sensory input via the dorsal nerve of the penis. SCI may disrupt the normal nerve pathways required for antegrade ejaculation. Approximately 9% of men with SCI are capable of ejaculation via masturbation or intercourse.¹⁷ Thus, the majority of men with SCI require medical assistance to induce an ejaculation. The 2 major options for sperm retrieval in men with SCI are penile vibratory stimulation (PVS) and electroejaculation (EEJ). If both of these methods fail, surgical sperm retrieval may be used.

PVS is an excellent option for patients with a level of injury T10 or rostral due to intact sympathetic and parasympathetic components of the ejaculatory reflex, as well as the dorsal nerve of the penis. The FertiCare personal (Multicept A/S, DK, Frederiksberg C, Denmark)

was the first US Food and Drug Administration (FDA)–approved electromechanical vibrator designed specifically to induce ejaculation in men with SCI; it was made available in 1995. The Viberec-X3 (Reflexonic, Frederick, MD) was recently developed and FDA-approved for assisted ejaculation in men with SCI using 2 vibrating pads to stimulate the penis (**Figure 1**).¹⁸

There are several steps prior to performing PVS to optimize the safety and efficacy of the procedure. The testing of 2 predictive reflexes, the bulbocavernosus response and the hip flexor response, prior to initial stimulation may serve as a good predictor of ejaculation by PVS. Patients with a level of injury T6 or rostral should be pretreated with nifedipine to prevent AD. An automatic vital signs monitor should be used throughout the procedure to monitor heart rate and blood pressure at 1-minute intervals. If retrograde ejaculation is expected, the bladder should be prepared accordingly. It should first be emptied by urinary catheterization, and then 25 to 50 mL of sperm washing medium should be instilled in the bladder immediately prior to stimulation. The sperm washing medium decreases urinary acidity. This preparation aims at increasing the number of motile and viable sperm in the retrograde ejaculate by attempting to improve the bladder environment to which the sperm are exposed.¹⁹

To perform PVS, the patient may be in his preferred position of supine, reclining, or sitting. Two persons are typically needed to perform the procedure, as one must apply the vibrator

and the other must hold a sterile specimen cup to collect any antegrade ejaculate. Some patients may feel more comfortable applying the vibrator themselves. The vibrator should be placed on the dorsum or frenulum of the glans penis. Stimulation is applied for a maximum of 2-minute intervals and stopped if there is no ejaculation. After each interval, it is important to examine the penile skin for early detection of skin abrasions or edema, which will warrant termination of the stimulation session. Additional 2-minute intervals of stimulation may be administered until an ejaculate is produced or until 15 minutes of stimulation have been administered with no ejaculation. The typical response time is 3 minutes or less. If ejaculation does not occur with one FertiCare device, 2 FertiCare devices may be applied. One vibrator should be applied on the dorsum and one placed on the frenulum of the glans penis. This has been shown to salvage up to 22% of failures to one device (**Figure 2**).²⁰ Viberec-X3 may also be used for simultaneous dorsal and frenular stimulation; however, patient satisfaction scores are lower for the Viberec-X3 than for 2 FertiCare devices.²¹

Some extragenital somatic responses may be seen in reaction to PVS, and these indicate that ejaculation is imminent. Increased spasticity below the level of injury and tightening of the abdominal and/or intercostal muscles may occur. As the stimulation progresses, the abdominal contractions become more rhythmic, more frequent, and more forceful. Although a firm

Figure 1. Devices for penile vibratory stimulation (PVS). Ejaculation may be induced by PVS in anejaculatory men with spinal cord injury. Two commercial devices are available for this purpose: the Viberec X-3 (left panel) and the FertiCare personal (right panel).

Figure 2. Application of 2 vibrators. Patients who fail to respond to the application of 1 vibrator may be salvaged with the application of 2 vibrators. The vibrators should be applied as shown, with one placed on the dorsum and one placed on the frenulum of the glans penis. Reprinted, with permission, from Brackett NL, Kafetsoulis A, Ibrahim E, Aballa TC, Lynne CM. Application of 2 vibrators salvages ejaculatory failures to 1 vibrator during penile vibratory stimulation in men with spinal cord injuries. *J Urol.* 2007;177(2):660-663. Copyright © 2007 Elsevier. <http://www.sciencedirect.com/science/journal/00225347>

erection may precede ejaculation, it is not always present. Following ejaculation, patients may experience periods of muscular flaccidity that can last from a few minutes to hours.²²

An 18-year single-center experience of 500 men with SCI reported an 86% success rate for PVS when the patient's level of injury was T10 or rostral and a 15% success rate when the patient's level of injury was T11 or caudal (**Figure 3**).¹⁷ The high success rate when the injury was rostral to T10 is most likely attributed to the integrity of all of the spinal cord components of the ejaculatory reflex.²³

Men with SCI who are unable to respond to PVS are often referred for EEJ as an alternative method of sperm retrieval. EEJ must be administered by a physician who is trained in this procedure. The only FDA-approved device for performing EEJ is the Seager Electroejaculator (Dalzell Medical Systems) (**Figure 4**). Prior to stimulation, patients whose level of injury is T6 or rostral are premedicated with nifedipine to prevent AD. The chance of retrograde ejaculation is higher with EEJ than PVS. Therefore,

bladder preparation is performed immediately before all EEJ procedures, as previously described. The patient is placed in the lateral decubitus position. A digital rectal examination and anoscopy may be performed prior to starting the procedure to ensure the integrity of the lower rectum and anus where the probe will be placed. Ejaculation is induced via electrodes positioned within the rectum and oriented toward the seminal vesicles and prostate gland. Electric current is applied in a pattern of gradually increasing voltage in 2-volt increments, holding the current at that cycle's peak for 5 seconds and then returning to 0 in this manner: 0 volts, 2 volts (hold 5 seconds), 0 volts (hold 10-20 seconds, look for ejaculate), 4 volts (hold x 5 seconds), 0 volts (hold x 10 seconds, look), 6 volts, and so on until an ejaculation occurs. Typically, ejaculation will occur during the time the current is turned off.²⁴ This on-off pattern of stimulation versus continuous delivery of stimulation has been shown to result in a higher proportion of sperm in the antegrade fraction.²⁵ Rectal temperature is monitored throughout the

Figure 3. Algorithm of semen retrieval in men with spinal cord injury (SCI). Sperm can be obtained nonsurgically from 97% of men with SCI. The algorithm is based on 3,152 semen retrieval procedures in 500 men with SCI. Penile vibratory stimulation (PVS) is recommended as the first line of treatment. If PVS fails, electroejaculation (EEJ) should be attempted. Surgical sperm retrieval (SSR) is a last resort if PVS and EEJ fail. Adapted, with permission, from Brackett NL, Ibrahim E, Iremashvili V, Aballa TC, Lynne CM. Treatment for ejaculatory dysfunction in men with spinal cord injury: An 18-year single center experience. *J Urol*. 2010;183(6):2304-2308. Copyright © 2007 Elsevier. <http://www.sciencedirect.com/science/journal/00225347>

procedure via a built-in sensor. Ejaculation may occur in a dribbling, nonprojectile manner. The assistant collecting the ejaculate should milk the urethra to retrieve as much semen as possible.

EEJ is successful in obtaining semen in nearly 100% of men with SCI. In the largest study of its kind to date, EEJ was performed 953 times in 210 patients. There was a 91.9% response rate to EEJ, and responders were consistent over consecutive

trials. Those who did not ejaculate with EEJ felt pain during the procedure and did not elect further trials under anesthesia.¹⁷

If PVS and EEJ yield no sperm in the antegrade or retrograde ejaculate, sperm may be obtained by removing tissue from reproductive structures. The reproductive structures used include the testis or the epididymis. Techniques used to surgically extract sperm include open testis biopsy, percutaneous

Figure 4. Electroejaculation device. Anejaculatory men with spinal cord injury who fail to respond to penile vibratory stimulation (PVS) may be referred for electroejaculation (EEJ). The EEJ device is shown here. The relative advantages and disadvantages of PVS versus EEJ are discussed in the text.

testicular biopsy, testicular sperm aspiration, percutaneous epididymal sperm aspiration, and microdissection testicular sperm aspiration.²⁶

Management of AD during ejaculation and/or orgasm

AD is an unregulated, uncontrolled sympathetic nervous system response to what is usually a noxious stimulus, but it can also occur from non-noxious stimuli.²⁷ AD occurs often in men with SCI who have levels of injury above T10. Lesions at this level or above effectively separate the nuclei of the sympathetic nervous system from all descending supraspinal controls. If AD occurs during sexual activity, the initial management consists of ceasing the sexual activity, using postural changes such as sitting up and lowering the feet, and removing any constrictive devices or clothing. If these measures do not mitigate the symptoms or drop the blood pressure satisfactorily (lower than 150 mm Hg of systolic blood pressure), medical management can be cautiously initiated. Couples should be counseled about the use of medications in managing acute episodes of AD; the

medications, if not carefully monitored, may lead to a precipitous drop in blood pressure.

Nifedipine is a calcium channel blocker that has been widely used in conjunction with PVS and EEJ for prophylaxis against severe AD during sperm retrieval. **Figure 5** shows a recording of cardiovascular responses during PVS. During PVS or EEJ, nifedipine is often given in a sublingual manner for rapid absorption a few minutes before starting the procedure. Pretreatment with a standard oral dose 1 hour before sexual activity is recommended. Nifedipine can also be used by couples to manage AD during sexual activity.

Although nifedipine is effective at significantly reducing the severity of blood pressure increases secondary to AD, some patients with SCI experience dizziness, fatigue, and weakness after being administered nifedipine. Nifedipine does have the risk of provoking severe hypotension.²⁸ Alternative therapies have been investigated for mitigating AD severity in the SCI population. A recent study

Figure 5. Cardiovascular responses during penile vibratory stimulation (PVS). Blood pressure (BP, top recording) and ECG (bottom recording) are shown for an individual with C6 AIS A SCI during a PVS procedure for sperm retrieval. Prior to PVS (*top recording), BP was registered as 100/50 mm Hg with regular heart rate of 82 bpm. With initiation of PVS (black solid line), arterial BP increased dramatically. At the time of ejaculation (**), BP reached up to 250/150 mm Hg with significant bradycardia (bottom recording; heart rate, 60 bpm). It is interesting to note that patient denied any symptoms typical for autonomic dysreflexia (AD) such as headache, blurred vision, sweating, and piloerection (unpublished data).

concluded that 1 mg prazosin administered orally once the night before and once 2 hours prior to ejaculation was effective at reducing the severity of iatrogenically induced AD in men with SCI undergoing PVS. Further, low resting blood pressure was not exacerbated by prazosin in SCI patients.²⁹

Nitrates can acutely reduce severe hypertension through their relaxation of smooth muscle in the peripheral vascular system. It is more effective to utilize nitrates in the transdermal paste form, which is more easily titratable, than in sublingual form. Prazosin is an alpha-1 blocker. It has been shown that a twice-daily dose exhibited minimal effect on cardiac function and mitigated the severity of AD episodes.²⁹⁻³¹

Many men with SCI have erectile dysfunction in the sense that they may have psychogenic or reflexogenic erections but these may not be sustained well enough or long enough for satisfactory intercourse. PDE-5i are effective in this situation and are widely used by men with SCI.^{12,13} Because PDE-5i have vasodilatory activity, there can be significant interactions between the medicines used for maintenance of erections and the medicines used to mitigate or prevent the severe effects of AD. Nitrates are contraindicated in persons using PDE-5i. The use of alpha blockers and PDE-5i increases the risks of clinically significant hypotension. The risk is lowest with tadalafil. The 2 medications should only be used together if the patient has been on a stable dose of the alpha blocker, and the doses of the 2 medicines should be separated by at least 4 hours.^{28,32}

Abnormal semen quality

The third obstacle in achieving the goal of biological fatherhood in men with SCI is the abnormal semen analysis parameters in this population. The characteristic semen profile of men with SCI includes normal sperm concentration but abnormally low sperm motility and viability. Factors that have been studied include lifestyle changes, method of sperm retrieval, seminal plasma biochemical alterations, and inflammatory and immunological changes.

After SCI, most men sit in a wheelchair for long periods of time. It has been hypothesized that this leads to scrotal hyperthermia, which subsequently leads to abnormal semen parameters. However, no studies to date have shown normalization of semen parameters with cooling the scrotum of men with SCI. Additionally, studies have shown that ambulatory men with SCI have similar abnormalities in their semen parameters.³³

Another lifestyle change after SCI is neurogenic voiding dysfunction. Studies have shown that clean intermittent catheterization is associated with a somewhat higher sperm motility than management by more invasive methods such as indwelling catheters. However, no method is associated with normal semen parameters, not even spontaneous voiding.³⁴

It has been hypothesized that anejaculation may lead to semen stasis, which may consequently lead to low sperm motility. The majority of studies, however, found no statistically significant improvement in sperm motility after regular ejaculation by PVS or EEJ.^{35,36} Also, no study has found normalization of sperm motility in men with SCI by increasing the frequency of ejaculation. These studies indicate that frequency of ejaculation is not the sole factor causing low sperm motility in men with SCI.

Sperm retrieval methods have been studied as possible causes of abnormal semen analysis parameters in men with SCI. Ejaculates obtained by masturbation had higher sperm motility than ejaculates obtained by PVS or EEJ. However, semen parameters remained abnormal in all 3 methods.³⁷

The accessory glands (ie, the prostate and seminal vesicles) contribute the majority of volume to seminal fluid. They share much of the same innervation as the bladder and penis. Thus, it is been hypothesized that SCI leads to abnormal innervation and function of these glands, which leads to abnormalities in the seminal plasma. This in turn contributes to low sperm motility. One study added seminal plasma from men with SCI to healthy sperm from noninjured men. The result was an immediate and profound decrease in sperm motility, clarifying the role of seminal plasma in abnormal sperm motility in men with SCI.³⁸ The role of seminal plasma was further

indicated in a study that found higher motility in sperm aspirated from the vas deferens of men with SCI compared to sperm in the ejaculates of those same men.³⁹

A common finding in seminal plasma of men with SCI is leukocytospermia. Analysis of semen in men with SCI shows elevated pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF- α .⁴⁰ Neutralization of these cytokines has led to improved sperm motility.^{41,42} The inflammasome is a platform of proteins that when triggered, assembles and initiates a cytokine cascade that is seen in the innate immune process. Components of the inflammasome have been investigated, and caspase-1 and ASC were found to be elevated in semen of men with SCI.⁴³ In vitro neutralization of ASC significantly improved sperm motility in these men.⁴⁴

Reproductive Options for Couples with SCI-Related Male Factor Infertility

Advances in assisted reproductive technologies (ARTs) have made biological parenthood a reality for many couples. Infertility treatments that are available to the general infertile population are available to couples in which the male partner has SCI. It is important to remember that female factor infertility may also be present as in any couple presenting for infertility. Thus, it is crucial that the female partner also be fully evaluated prior to any attempt at assisted conception. If there is no female factor to infertility, the type of ART chosen should be based on the number of motile sperm available. The hierarchy of methods of sperm retrieval are masturbation, PVS, EEJ, and surgical sperm retrieval. The lower the total motile sperm count, the more advanced the technology that will be recommended for successful conception.

Intravaginal insemination, or in-home insemination, is the least expensive and the closest to natural conception of the currently available ART techniques. The insemination is timed to the woman's ovulatory cycle, which is usually determined with an over-the-counter ovulation monitoring kit. After collection of semen into a nonsterile specimen cup, the semen is drawn up in a 3 cc or 5 cc syringe. The

syringe (with no needle) is gently inserted into the vagina, and the semen is deposited by advancing the plunger of the syringe. A study of 140 couples between 1988 and 2008 reported a 43% pregnancy rate using intravaginal insemination. Other studies in couples with a male partner with SCI report success rates of this method ranging from 25% to 70%.⁴⁵

Intrauterine insemination (IUI) is the next option if multiple intravaginal insemination attempts have failed. IUI can also be successful and cost-effective in couples with SCI male partners. Semen is obtained using PVS or EEJ. The sample is then processed to remove the seminal plasma and to concentrate the sperm pellet to approximately 0.5 mL. Sperm are introduced into the uterine cavity using a fine cannula. The IUI cycle can be performed with or without ovarian stimulation.⁴⁶

There is a lack of consensus regarding the lower limit of total motile sperm count for considering IUI. If total motile sperm count is lower than the treating center's guidelines for IUI, then in vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI) is the method of choice. IVF/ICSI requires surgical sperm retrieval, therefore making this the most expensive and invasive option. Multiple studies have shown pregnancy success rates with IVF/ICSI for couples with an SCI male partner to be similar to those reported for couples with other male factor etiologies. For example, one study showed a pregnancy rate of 58.1% per SCI couple and 57.9% per non-SCI couple, which is not a significant difference.⁴⁷

Conclusions

Men with SCI face obstacles when pursuing sexual activity and/or biologic fatherhood. Hypogonadism and premature symptoms of aging may interfere with sexual function. Erectile dysfunction is prevalent in the SCI population. Treatments for erectile dysfunction in the general population are also effective in the SCI population. Most men with SCI cannot ejaculate with sexual intercourse. Medical assistance is necessary to retrieve semen for assisted conception. A management algorithm for ejaculatory dysfunction

has been recommended that allows for nonsurgical semen retrieval in 97% of men with SCI. Semen quality is abnormal in most men with SCI. Although sperm concentration is typically normal, sperm motility and viability are abnormally low. The cause of this condition is an active area of research and seems to be related to factors in the seminal plasma. Management of infertility in a couple with a male partner with SCI should include an evaluation of both the male and female

partners. The semen quality of the male partner with SCI should be assessed. With sufficient total motile sperm, the assisted conception procedures of intravaginal insemination or IUI should be considered prior to referring the couple for surgical sperm retrieval or IVF/ICSI.

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REFERENCES

1. National SCI Statistical Center. Spinal Cord Injury (SCI) Facts and Figures at a Glance. *J Spinal Cord Med.* 2016;39(3):370-371.
2. Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: Clinical practice guideline. *CMAJ.* 2015;187(18):1369-1377.
3. Bauman WA, La Fountaine MF, Cirnigliaro CM, Kirshblum SC, Spungen AM. Lean tissue mass and energy expenditure are retained in hypogonadal men with spinal cord injury after discontinuation of testosterone replacement therapy. *J Spinal Cord Med.* 2015;38(1):38-47.
4. Durga A, Sepahpanah F, Regozzi M, Hastings J, Crane DA. Prevalence of testosterone deficiency after spinal cord injury. *PM & R.* 2011;3(10):929-932.
5. Chiodo AE, Sitrin RG, Bauman KA. Sleep disordered breathing in spinal cord injury: A systematic review. *J Spinal Cord Med.* 2016;39(4):374-382.
6. Eklund MB, Krassioukov AV, McBride KE, Elliott SL. Incidence of autonomic dysreflexia and silent autonomic dysreflexia in men with spinal cord injury undergoing sperm retrieval: Implications for clinical practice. *J Spinal Cord Med.* 2008;31(1):33-39.
7. Jegede AB, Rosado-Rivera D, Bauman WA, et al. Cognitive performance in hypotensive persons with spinal cord injury. *Clin Auton Res.* 2010;20(1):3-9.
8. Yeh TS, Huang YP, Wang HI, Pan SL. Spinal cord injury and Parkinson's disease: A population-based, propensity score-matched, longitudinal follow-up study. *Spinal Cord.* 2016;54(12):1215-1219.
9. Ibrahim E, Lynne CM, Brackett NL. Male fertility following spinal cord injury: An update. *Andrology.* 2016;4(1):13-26.
10. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol Clin North Am.* 2005;32(4):379-395.
11. Everaert K, de Waard WI, Van Hoof T, Kiekens C, Mulliez T, D'Herde C. Neuroanatomy and neurophysiology related to sexual dysfunction in male neurogenic patients with lesions to the spinal cord or peripheral nerves. *Spinal Cord.* 2010;48(3):182-191.
12. Rizio N, Tran C, Sorenson M. Efficacy and satisfaction rates of oral PDE5is in the treatment of erectile dysfunction secondary to spinal cord injury: A review of literature. *J Spinal Cord Med.* 2012;35(4):219-228.
13. Lombardi G, Nelli F, Celso M, Mencarini M, Del Popolo G. Treating erectile dysfunction and central neurological diseases with oral phosphodiesterase type 5 inhibitors. Review of the literature. *J Sex Med.* 2012;9(4):970-985.
14. Giuliano F, Rubio-Aurioles E, Kennelly M, et al. Vardenafil improves ejaculation success rates and self-confidence in men with erectile dysfunction due to spinal cord injury. *Spine.* 2008;33(7):709-715.
15. Lombardi G, Musco S, Wyndaele JJ, Popolo GD. Treatments for erectile dysfunction in spinal cord patients: Alternatives to phosphodiesterase type 5 inhibitors? A review study. *Spinal Cord.* 2015;21(10):116.
16. Elliott S. Case study: Erectile dysfunction following spinal cord injury. *J Sex Med.* 2010;7(12):3808-3814.
17. Brackett NL, Ibrahim E, Iremashvili V, Aballa TC, Lynne CM. Treatment for ejaculatory dysfunction in men with spinal cord injury: An 18-year single center experience. *J Urol.* 2010;183(6):2304-2308.
18. Castle SM, Jenkins LC, Ibrahim E, Aballa TC, Lynne CM, Brackett NL. Safety and efficacy of a new device for inducing ejaculation in men with spinal cord injuries. *Spinal Cord.* 2014;52(suppl 2):S27-S29.
19. Suominen JJ, Kilkku PP, Taina EJ, Puntala PV. Successful treatment of infertility due to retrograde ejaculation by instillation of serum-containing medium into the bladder. A case report. *Int J Androl.* 1991;14(2):87-90.
20. Brackett NL, Kafetsoulis A, Ibrahim E, Aballa TC, Lynne CM. Application of 2 vibrators salvages ejaculatory failures to 1 vibrator during penile vibratory stimulation in men with spinal cord injuries. *J Urol.* 2007;177(2):660-663.
21. Chong W, Ibrahim E, Aballa T, Lynne C, Brackett NL. Comparison of three methods of penile vibratory stimulation (PVS) in men with spinal cord injury (SCI). *Fertil Steril.* 104(3):e8.

22. Laessoe L, Sonksen J, Bagi P, et al. Effects of ejaculation by penile vibratory stimulation on bladder reflex activity in a spinal cord injured man. *J Urol.* 2001;166(2):627.
23. Wieder J, Brackett N, Lynne C, Green J, Aballa T. Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. *Urology.* 2000;55(16):915-917.
24. Sonksen J, Ohl DA, Wedemeyer G. Sphincteric events during penile vibratory ejaculation and electroejaculation in men with spinal cord injuries. *J Urol.* 2001;165:426-429.
25. Brackett NL, Ead DN, Aballa TC, Ferrell SM, Lynne CM. Semen retrieval in men with spinal cord injury is improved by interrupting current delivery during electroejaculation. *J Urol.* 2002;167(1):201-203.
26. Schlegel PN. Nonobstructive azoospermia: A revolutionary surgical approach and results. *Semin Reprod Med.* 2009;27(2):165-170.
27. Partida E, Mironets E, Hou S, Tom VJ. Cardiovascular dysfunction following spinal cord injury. *Neural Regen Res.* 2016;11(2):189-194.
28. Krassioukov A, Warburton DE, Teasell R, Eng JJ. A systematic review of the management of autonomic dysreflexia after spinal cord injury. *Arch Phys Med Rehabil.* 2009;90(4):682-695.
29. Zheng MM, Phillips AA, Elliott SL, Krassioukov AV. Prazosin: A potential new management tool for iatrogenic autonomic dysreflexia in individuals with spinal cord injury? *Neural Regen Res.* 2015;10(4):557-558.
30. Phillips AA, Elliott SL, Zheng MM, Krassioukov AV. Selective alpha adrenergic antagonist reduces severity of transient hypertension during sexual stimulation after spinal cord injury. *J Neurotrauma.* 2015;32(6):392-396.
31. Krum H, Louis WJ, Brown DJ, Howes LG. A study of the alpha-1 adrenoceptor blocker prazosin in the prophylactic management of autonomic dysreflexia in high spinal cord injury patients. *Clin Auton Res.* 1992;2(2):83-88.
32. Schwartz BG, Kloner RA. Drug interactions with phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. *Circulation.* 2010;122(1):88-95.
33. Brackett NL, Lynne CM, Weizman MS, Bloch WE, Padron OF. Scrotal and oral temperatures are not related to semen quality or serum gonadotropin levels in spinal cord-injured men. *J Androl.* 1994;15: 614-619.
34. Rutkowski SB, Middleton JW, Truman G, Hagen DL, Ryan JP. The influence of bladder management on fertility in spinal cord injured males. *Paraplegia.* 1995;33(5):263-266.
35. Siosteen A, Forssman L, Steen Y, Sullivan L, Wickstrom I. Quality of semen after repeated ejaculation treatment in spinal cord injury men. *Paraplegia.* 1990;28:96-104.
36. Sonksen J, Ohl DA, Giwerzman A, Biering-Sorensen F, Skakkebaek NE, Kristensen JK. Effect of repeated ejaculation on semen quality in spinal cord injured men. *J Urol.* 1999;161(4):1163-1165.
37. Kathiresan AS, Ibrahim E, Modh R, Aballa TC, Lynne CM, Brackett NL. Semen quality in ejaculates produced by masturbation in men with spinal cord injury. *Spinal Cord.* 2012;50(12):891-894.
38. Brackett NL, Davi RC, Padron OF, Lynne CM. Seminal plasma of spinal cord injured men inhibits sperm motility of normal men. *J Urol.* 1996;155:1632-1635.
39. Brackett NL, Lynne CM, Aballa TC, Ferrell SM. Sperm motility from the vas deferens of spinal cord injured men is higher than from the ejaculate. *J Urol.* 2000;164:712-715.
40. Basu S, Aballa TC, Ferrell SM, Lynne CM, Brackett NL. Inflammatory cytokine concentrations are elevated in seminal plasma of men with spinal cord injuries. *J Androl.* 2004;25(2):250-254.
41. Brackett NL, Cohen DR, Ibrahim E, Aballa TC, Lynne CM. Neutralization of cytokine activity at the receptor level improves sperm motility in men with spinal cord injuries. *J Androl.* 2007;28(5):717-721.
42. Cohen DR, Basu S, Randall JM, Aballa TC, Lynne CM, Brackett NL. Sperm motility in men with spinal cord injuries is enhanced by inactivating cytokines in the seminal plasma. *J Androl.* 2004;25:922-925.
43. Zhang X, Ibrahim E, Rivero Vaccari JP, et al. Involvement of the inflammasome in abnormal semen quality of men with spinal cord injury. *Fertil Steril.* 2013;99(1):118-124.
44. Ibrahim E, Castle SM, Aballa TC, et al. Neutralization of ASC improves sperm motility in men with spinal cord injury. *Hum Reprod.* 2014;29(11):2368-2373.
45. Sonksen J, Fode M, Lochner-Ernst D, Ohl DA. Vibratory ejaculation in 140 spinal cord injured men and home insemination of their partners. *Spinal Cord.* 2012;50(1):63-66.
46. Zhao Y, Vlahos N, Wyncott D, et al. Impact of semen characteristics on the success of intrauterine insemination. *J Assist Reprod Genet.* 2004;21(5): 143-148.
47. Kathiresan AS, Ibrahim E, Aballa TC, et al. Comparison of in vitro fertilization/intracytoplasmic sperm injection outcomes in male factor infertility patients with and without spinal cord injuries. *Fertil Steril.* 2011;96(3):562-566.