Management of Male Infertility After Spinal Cord Injury

Jens Sønksen and David Chen

Ejaculatory dysfunction and impairment of semen quality are commonly found in men after spinal cord injury (SCI). Each condition alone and in combination has the potential to interfere with the ability of the individual and his partner to have children. Over the past several decades, clinical treatments and techniques have been developed and advances in assisted reproductive techniques have taken place that now allow spinal cord-injured men to father children. This review will focus on the current understanding of ejaculatory dysfunction, semen characteristics, and clinical treatments and techniques to enhance fertility in men with SCI. Key words: *ejaculatory dysfunction, male fertility, spinal cord injury*

In the past, it was a common belief that men with spinal cord injury (SCI) were permanently impotent and incapable of having children. Therefore, these individuals and their partners were required to consider other means, such as adoption or donor sperm, in order to have families. Over the past several decades through research, clinical investigations, development of adaptive techniques/modalities, and advances in assisted reproductive techniques, this belief is no longer a reality and men with SCI are having children and raising families.

Frequently, questions and inquiries regarding future ability to have children will arise early in the acute hospital course or during acute rehabilitation after SCI. It is vital therefore for health care providers to have an understanding of this aspect of a person's SCI condition and potential clinical treatments so that they can give appropriate information and education to the spinal cord-injured person, his partner, and family.

This review will focus on the present knowledge regarding ejaculatory dysfunction, semen characteristics, and techniques to enhance fertility in spinal cord-injured men.

Normal Ejaculation

Efferent sympathetic fibers originating from T11-L2 innervate the vas deferens, seminal vesicles, and prostate smooth muscle fibers via the hypogastric nerve and are responsible for the peristalsis necessary for seminal emission, the first phase of ejacu-

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lation. Closure of the bladder neck also occurs through sympathetic stimulation.

Efferent parasympathetic fibers from S2-4 innervate the prostate gland, which contributes to the formation of seminal fluid.

The pudendal nerve (S2-4) innervates the bulbospongiosus and ischiocavernosus muscles and the muscles of the pelvic floor that are responsible for the clonic contractions causing the projectile ejaculation with release of semen from the urethra, which is the second phase of ejaculation or ejaculation proper. Therefore, if a man has an injury to the S2-4 level, the ejaculation is not projectile, but dribbling in nature.

Ejaculation After SCI and Management

The ability to procreate naturally is significantly impaired in the majority of men with SCI due to ejaculatory dysfunction and abnormal semen characteristics.[1–3] There are numerous studies that report a low percentage of men who are able to ejaculate normally after SCI. In a review of the literature, Higgins[4] reported the ability to ejaculate in less than 10% of men with complete injuries and in 32% of men with incomplete injuries. In another review of the literature, which included 2,527 men with SCI, Sønksen and Biering-Sørensen[2] reported that the ability to ejaculate during sexual stimulation or masturbation ranged from 0% to 55% (median 15%).

To manage the issue of ejaculatory dysfunction in men with SCI, several methods of assisted ejaculation have been used including intrathecal and subcutaneous administration of cholinesterase inhibitors, rectal electroejaculation (EEJ), and penile vibratory stimulation (PVS).[2]

Cholinesterase inhibitors

In 1946, Guttmann[5] was the first to use intrathecal injection of cholinesterase inhibitors, which resulted in several spontaneous ejaculations over several hours. Unfortunately, many adverse autonomic side effects also occurred, such as paroxysmal changes in the blood pressure, sweating, and flushing. One death has been reported from malignant hypertension and cerebral hemorrhage with the use of this technique in a person with SCI.[6] Because of this substantial risk to the patient, intrathecal injection of cholinesterase inhibitors has been widely abandoned in the management of ejaculatory dysfunction.

To decrease the autonomic side effects of intrathecal administration of cholinesterase inhibitors, subcutaneous administration has been suggested by Chapelle et al.[7] This requires additional penile stimulation by masturbation or vibration to induce ejaculation. Subcutaneous administration of cholinesterase inhibitors may still cause parasympathetic side effects such as nausea, vomiting, abdominal cramps, and diarrhea.[7] With alternative procedures readily available, such as PVS and rectal EEJ, subcutaneous administration of cholinesterase inhibitors is rarely used and generally is not recommended as the first choice of treatment.[8]

Electroejaculation

Rectal EEJ has been one of the most frequently used treatments for ejaculatory dysfunction in men with SCI for many years. EEJ was first described in humans by Learmonth in 1931.[9] In 1948, Horne et al.[10] reported the first use of EEJ in SCI persons, resulting in successful ejaculation in 9 out of 15 men. In the 1980s, Seager et al.[11] further

refined the method of EEJ and developed several prototypes of equipment.

EEJ is performed with an electrical probe, which is inserted rectally and is positioned with the electrodes in contact with the anterior rectal wall in the area of the prostate gland and the seminal vesicles. The electrical stimulation is administered in a wave-like pattern with voltage progressively increasing in 1-2 V increments until ejaculation occurs.[8,11,12] It is usually recommended that a low level of electrical baseline (100 mA) be maintained between voltage peaks and during ejaculation. However, in a recent study concerning sphincteric events during EEJ and PVS in men with SCI, it was suggested that it would be optimal in EEJ procedures to discontinue electrical stimulation completely during ejaculation to allow greater relaxation of the external urethral sphincter, which may increase the percentage of semen ejaculated in the antegrade direction.[13,14]

The fraction of antegrade ejaculate is not produced as a projectile ejaculation, but rather as an intermittent release of semen during the course of the procedure.[11,15] Between 15–35 stimulations are usually needed to ensure emptying of the semen.[11] The voltages and currents that have been reported to successfully produce ejaculation range from 5–25 V and 100–600 mA, respectively.[12,16]

Prior to the EEJ procedure, the patient's bladder is catheterized to completely empty it of urine, because many individuals have a substantial portion of retrograde ejaculation.[16] Because urine may adversely affect this retrograde ejaculate, a buffering medium (e.g., Ham's F 10 medium) can be instilled into the bladder before the EEJ.[17,18] After the procedure, the bladder is catheterized again to empty the retrograde fraction. Rectoscopy is performed prior to and after the procedure to confirm that there are no preexisting rectal lesions and to exclude injury to the rectum from the procedure, respectively.

It should be noted that EEJ can cause significant discomfort in men with partly preserved sensation, and they may require either a spinal or general anaesthesia before treatment.[15,18–20] In addition, EEJ may produce autonomic dysreflexia in men with injuries above T6.[21] Blood pressure monitoring should be performed throughout the procedure; men who are susceptible to autonomic dysreflexia or who have experienced episodes with prior trials of EEJ may be premedicated with nifedipine or nitropaste.[22]

EEJ may be successful in obtaining ejaculate from men with all types of SCI, including men who are missing major components of the ejaculatory reflex arc.[18] In a prospective study by Ohl et al.,[16] predictors of success in relation to the response of 48 men with SCI to EEJ were studied. In relation to successful EEJ, they found no significant difference between men with SCI with high versus low or complete versus incomplete spinal cord lesions. Ejaculation was produced in 60% of cervical patients compared to 50% of lumbar patients. Ejaculation was seen in 71% of men with complete lesions and in 61% with incomplete lesions. However, more recent studies show that it is possible to induce ejaculation with EEJ in 80%–100% of all men with SCI.[18,23–26]

Penile vibratory stimulation

PVS to induce ejaculation was first described in 1965 by Sobrero et al.[27] in a group of men without SCI. The first reported use of PVS in a man with an SCI was with a hand

massager.[28] A number of investigators have reported successful results in achieving ejaculations with PVS, but Brindley has been credited with refining the technique most frequently used with PVS in men with SCI. In his initial studies, Brindley[29] reported successful ejaculation in 48 of 81 men with SCI.

The PVS procedure is performed with the individual in the supine position or in a sitting position in the wheelchair.[30] The goal of PVS is to activate the ejaculatory reflex; the afferent penile dorsal nerve stimulation is provided by application of a vibrating disc against the frenulum for periods of 2½ to 3 minutes or until antegrade ejaculation occurs. If no ejaculation occurs, the stimulation period is followed by a rest period of 1–2 minutes and stimulation begins again. An antegrade ejaculation occurs as a pulsatile projectile ejaculation similar to normal ejaculation. In contrast to EEJ, nearly all spermatozoa in PVS trials are ejaculated in the antegrade direction.[31] The required time to induce ejaculation by PVS ranges from 10 seconds to 45 minutes.[32–34] During PVS, somatic reactions such as erections, abdominal muscle contractions, and leg spasms may be seen.[33]

In contrast to EEJ, PVS seems to require an intact spinal cord at the level of T11-S4 in order to induce antegrade ejaculation.[29,32,33] However, the data from Brindley's study concerning the exact level and completeness of spinal cord lesion in relation to the ejaculatory response is unclear.[29] Szasz and Carpenter[33] reported from their work that the level and completeness of the spinal cord lesion could not predict with certainty successful ejaculation by PVS in a group of 35 men with SCI.

Furthermore, Brindley[29] noted that the most important factor indicating whether or not an ejaculate could be obtained by PVS was the clinical presence or absence of the hip flexion reflex (L2-S1), which is elicited by scratching the soles of the feet. Ejaculation was obtained in 75% of men with SCI who had an intact hip flexion reflex and in no men who did not have the hip flexion reflex. However, it should be noted that 25% of the men with SCI who had the clinical presence of the hip flexion reflex failed to ejaculate by PVS. Szasz and Carpenter[33] noted that the absence of the bulbocavernous reflex (S2-S4) predicted no ejaculatory response by PVS in most men with SCI.

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Although there are no clearly defined or standardized parameters for the application of PVS in men with SCI, it has been suggested that the output of the vibrators and, in particular, the amplitude might have some effect on the ejaculatory response.[29,33] In fact, a wide range of ejaculation rates (19%–91%) has been reported in the literature and may be due to the fact that several nonmedical vibrators have been used and the output from these vibrators may vary widely and are not standardized.[20,29,32–40]

Sønksen et al.[41] examined the ejaculatory response in men with SCI to varying amplitudes of PVS and found that the highest rates of ejaculation (antegrade plus retrograde) were seen with a vibrator amplitude level of

2.5 mm and a frequency of 100 Hz (96%), and low rates were seen when the amplitude was only 1 mm (32%). Sønksen et al. verified the effectiveness of the high amplitude vibration in the same study by obtaining an ejaculation rate of 83% in another comparable group of 41 spinal cord-injured men with ejaculatory dysfunction.

In the same study, antegrade ejaculation was seen only in men with cord lesions above T10, and no other absolute predictors of the ejaculatory response were identified among patient characteristics related to reflexes, completeness of lesions, somatic reactions, age, and time since SCI.[41] However, when the reflexes and/or somatic reactions such as erections, abdominal muscle contractions, and leg spasms were present during PVS, there was a significantly higher percentage of men with antegrade ejaculation compared to those men in whom none of the reflexes and/or somatic reactions were seen.

In general, PVS is a well-tolerated procedure with very few potential complications. Local skin abrasion may occur on occasion where the vibrator is applied, but no special treatment is usually required other than relief from further irritation. In men with neurologic levels at or above T6, the application of PVS may induce autonomic dysreflexia, if they are prone to this condition.[21,42] As in EEJ treatment, the individual may be premedicated with nifedipine or nitropaste prior to the procedure to minimize the blood pressure elevation and symptoms. Blood pressure monitoring should be performed during the procedure, especially in men prone to or with a history of autonomic dysreflexia.

Surgical sperm retrieval

If assisted ejaculation procedures fail or yield insufficient motile and/or viable spermatozoa for assisted reproductive techniques, surgical procedures for sperm retrieval are indicated. However, the man with SCI should be evaluated (as if he had no neurologic lesion) for obstructive as well as nonobstructive causes of the problem before any invasive procedure is performed.[43]

Successful sperm retrieval from vas deferens and from implanted sperm reservoirs has been reported in men with SCI.[44–47] Brindley et al.[48] reported an additional method to induce an ejaculate through direct stimulation of the hypogastric nerve using an implanted nerve stimulator. One pregnancy has been reported that was achieved using spermatozoa aspirated directly from the testicle or epididymis combined with intracytoplasmic sperm injection in an in vitro fertilization cycle.[49]

Although the surgical techniques are relatively easy to perform, an effective nonsurgical method is preferable.[1]

Fertility

Although the majority of men with SCI are able to produce an ejaculate with PVS or EEJ, the ability to procreate remains a challenge due to abnormal semen characteristics that are commonly found in these persons.[2] However, successful pregnancies in partners of men with SCI have been reported through the use of either vaginal home insemination or various methods of assisted reproduction techniques.[50]

Semen quality

Semen analyses data from ejaculates obtained without therapeutic assistance in men with SCI are virtually nonexistent, but one early publication by Horne et al.[10] reported the analysis of semen obtained by masturba-

tion in three men with SCI. They found total motile sperm counts between 30 and 110 millions (normal total sperm count > 40 millions, according to World Health Organization [WHO] standard criteria 1992).[51] In the man with the highest count, an additional specimen demonstrated a motility rate of 26% (normal motility rate > 50%). However, nearly all data concerning semen analyses in men with SCI are from ejaculates induced by PVS or EEJ; the semen is, in general, characterized by normal-to-high sperm count and low sperm motility rates compared to normal standards.[16,20,25,29,31,34,38,51–54]

Several theories have been suggested to explain the impaired sperm motility in men with SCI, including urinary tract infections, type of urinary bladder management, abnormal testicular histology, testicular hyperthermia, changes in the sex hormonal profiles, antisperm antibodies, and sperm stagnation in the seminal ducts due to anejaculation.[1] In addition, recent work has suggested that the method of semen retrieval (EEJ vs. PVS) may have a significant impact on sperm quality.[55]

It is well known that there is a high incidence of urinary tract infection in persons with SCI.[56] Recurrent infections may lead to epididymitis and epididymo-orchitis, which can impair semen profiles by leading to obstruction of the epididymal ducts or atrophy of the testicles.[8] The effects of urinary tract infection on EEJ semen characteristics have been studied in chronic SCI individuals, and no significant effect on semen characteristics was seen in ejaculates from men with SCI with infected urine compared to men without infections.[57] It was reported that the sperm motility rates were better in men with SCI who performed intermittent catheterization or who had undergone sphincterotomy for bladder emptying compared to those men who managed their bladders with an indwelling catheter or high pressure reflex voiding (27% and 25% vs. 5% and 15%, respectively).[16] It has also been demonstrated on video-urodynamics that men with SCI who use reflex voiding and who generally have a higher voiding pressure may have reflux of urine into the ejaculatory ducts that may lead to chronic inflammation in the reproductive organs and reduced sperm motility.[16] Furthermore, when Rutkowski et al.[53] looked at a number of spinal cord-injured men with the presence of motile sperm obtained from both PVS and EEJ ejaculates, they reported that intermittent catheterization was superior to other methods of bladder management.

Changes in testicular histology have been noted in men with SCI. Hirsch et al.[58] demonstrated a significantly lower mean spermatid count and higher Sertoli cell count per seminiferous tubule and a higher Sertoli cell/spermatid ratio when compared to normal, fertile controls. In other studies, abnormal as well as normal testicular histology has been found.[19,59–61]

Elevated scrotal temperatures have been reported to decrease spermatogenesis, and it has been suggested that this may be an issue in men with SCI who sit in their wheelchairs for a large part of the day.[62] In men with SCI, both elevated and unchanged scrotal temperatures compared to noninjured controls have been described.[63–65]

Reports on sexual hormone profiles in men with SCI have been conflicting.[19,60,66–73] Serum levels of testosterone, follicle-stimulating hormone, and luteinizing hormone have been found normal, above normal, and below normal after SCI when compared to laboratory standards and controls, respectively. Although changes in sex hormone

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Antisperm antibodies are believed to adversely influence male fertility, and men with SCI may be predisposed to conditions associated with the development of antisperm antibodies such as recurrent urinary tract infection leading to epididymitis and epididymal obstruction.[19,74–77] The presence as well as absence of antisperm antibodies in serum, seminal fluid, and on the surface of spermatozoa has been demonstrated in men with SCI.[78–82] No significant correlation between semen characteristics and antisperm antibodies has been documented, but it was suggested that sperm antibodies in the seminal fluid may play a negative role in relation to sperm function in men with SCI.[81]

Another theory that has been frequently discussed is stagnation of spermatozoa in the genital ducts from anejaculation, which leads to the presence of large numbers of senescent spermatozoa in the ejaculate and, consequently, to poor sperm motility.[1] One solution to this problem in men with SCI would be induction of ejaculation on a regular basis. Previous work has shown some improvement of semen parameters in men with SCI after frequent PVS ejaculation for variable periods of 3 to 6 months.[34,38] However, in a recent study, 19 men with SCI were followed for an entire year of frequent ejaculation, which represents the longest follow-up in such a study to date.[83] None of the semen parameters improved in this study, which suggests that stagnation in the seminal ducts due to infrequent ejaculation is not the etiology of the impaired sperm motility rates seen in men with SCI. Although some of the aforementioned factors may play a role for abnormal semen characteristics in chronic men with SCI, it appears that none are the sole cause of the problem and the etiology may be multifactorial.

Differences in semen profiles from the use of EEJ and PVS in men with SCI and, in particular, the potential damaging effects of EEJ on semen profiles have been discussed in the literature.[1,29] In one prospective study of 11 men with SCI, it was shown that the motility rate of PVS-induced antegrade sperm was significantly better than that of EEJ-induced antegrade sperm, even though the motility rates were subnormal with both methods.[84] This difference in sperm motility rates may be due to the effect of chronic denervation caused by SCI rather than to the method of assisted ejaculation. However, a similar significant difference between PVS and EEJ has been shown in the antegrade sperm motility rates in a nonhuman spinal cord-intact primate model.[85] This may indicate that the EEJ method itself may compromise the sperm motility rate in antegrade ejaculates; this should be taken into consideration when fertility and semen characteristics are studied in men with SCI.

In another study including 51 men with SCI, it was demonstrated that the completeness and level of lesion also influence the sperm motility. There were significantly higher motility rates in men with cervical versus thoracic lesions, lesions at or above

T6 versus below T6, and incomplete versus complete lesions, respectively.[54] This is in contrast to the EEJ study by Ohl et al.[16] where the sperm motility was highest in patients with thoracic lesions and the presence of motile sperm was more frequent in patients with complete lesions.

Recent investigations indicate that factors in the seminal plasma may contribute to the impaired sperm motility in men with SCI. For example, seminal plasma from ejaculates of men with SCI inhibited the motility of sperm from normal men, and seminal plasma from normal men improved the motility of sperm from men with SCI.[86] Furthermore, it was demonstrated that the viability and motility rate of ejaculated spermatozoa induced by PVS or EEJ was significantly lower than that of spermatozoa aspirated from the vas deferens in a group of men with SCI compared to non-SCI controls.[87]

Another recent study found that large numbers of senescent spermatozoa with poor motility and viability are present within the seminal vesicles of men with SCI, and these spermatozoa comprise a large portion of the ejaculates obtained by PVS and EEJ.[88] This indicates that men with SCI may have disordered storage of spermatozoa in the seminal vesicles, which leads to impaired quality of ejaculated semen.

More recently, it has been suggested that the method of assisted ejaculation that is used in men with SCI may affect the quantity and quality of sperm retrieved. Brackett and Lynne[55] have stated that antegrade specimens obtained by PVS are preferable for scientific applications in men with SCI. For clinical applications, such as harvesting sperm for assisted reproductive procedures, it is less critical whether semen is obtained by EEJ or PVS; however, semen obtained via PVS has been found to be higher in antegrade volume and higher in antegrade sperm motility and viability.

The acute effects of SCI on semen characteristics in humans have only been reported in one study. Mallidis et al.[89] used EEJ to obtain frequent ejaculates in seven men from Day 2 after an acute SCI. No decline in semen profiles was seen until Day 16. Thereafter, sperm motility and viability decreased toward the pattern seen in chronic men with SCI.

Very few other studies have examined the direct changes in spermatogenesis and semen characteristics during the acute phase of SCI. Billups et al.[90,91] demonstrated decreased epididymal sperm motility as well as disordered epididymal spermatozoa storage in a sympathectomized rat model. Huang and co-workers[92] performed SCI in a rat model to examine acute changes in spermatogenesis. Different groups of rats were sacrificed at various time points after SCI. Huang et al. found that significant decreases in spermatogenesis were seen several days after SCI and some recovery was noted after 6 months. Even though useful information was gained by these studies, these models lacked the ability to examine serial changes in spermatogenesis in the same animals and the ability to examine ejaculated semen characteristics rather than epididymal spermatozoa. To investigate these questions, Ohl et al.[93] developed a dog model of SCI that allowed serial examination of both semen profiles and spermatogenesis in the same animals. Data from this model has provided strong evidence for a decline in spermatogenesis and sperm motility at 3 weeks after SCI compared to non-SCI control dogs.

The mechanisms responsible for the im-

paired semen characteristics in men with SCI are still largely unknown; further studies are required to gain more insight into the impact of the autonomic nervous system on the production, transport, and storage of spermatozoa and the composition of biochemical substances in the seminal fluid. Also, studies of changes in spermatogenesis and semen characteristics from the acute period of SCI, through spinal shock, and into the chronic phase of SCI are necessary.

Management to Achieve Pregnancies

Home insemination

PVS and vaginal self-insemination performed by a couple at home is a viable option for men with SCI with adequate semen parameters.[25,29,50,94,95] The SCI man and his partner should be carefully instructed in the use of PVS through supervised procedures at the health care facility. Men with SCI at or above T6 are reminded about the issue of autonomic dysreflexia; in men for whom it is deemed necessary, the use of prophylactic nifedipine or nitropaste should be considered. A nonspermicidal container is used for collection of the ejaculate, and a 10-mL syringe is used for vaginal self-insemination.

In 1984, Brindley[29] reported seven home pregnancies after PVS and vaginal self-insemination with delivery of five healthy babies. More recently, there have been additional reports of successfully achieving pregnancies from PVS procedures combined with self-insemination in the home setting.[25,50,94,95] Most studies have reported that multiple ovulation cycles were required to achieve home pregnancies, and the overall pregnancy rate per couple ranged from 25% to 61%. The unique advantage of PVS is its potential for home use, and several devices are commercially available.

Assisted reproduction techniques

Recently, several successful pregnancies have been reported from spermatozoa obtained by PVS or EEJ combined with assisted reproduction techniques such as intrauterine insemination or in vitro fertilization with or without intracytoplasmic sperm injection.[25,50,52,64,95–98] The overall pregnancy rate per cycle from these studies is about 25%.[25,30,52,94–98] It should be noted that this rate is similar to the pregnancy rate per cycle during natural procreation in healthy couples attempting pregnancies (25%–30%).[99]

Summary

Despite changes in semen quality and impairment of ejaculatory function in men after SCI, treatments are readily available. With advances in assisted reproduction techniques, successful pregnancies can be achieved. It is important that health care providers have information on fertility issues and are aware of available treatments so that men with SCI and their partners can receive appropriate education and counseling.

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