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Abstract

Objective/Background: Neurogenic reproductive dysfunction in men with spinal cord injury (SCI) is common and the result of a combination of impotence, ejaculatory failure, and abnormal semen characteristics. It is well established that the semen quality of men with SCI is poor and that changes are seen as early as 2 weeks after injury. The distinguishing characters of poor quality are abnormal sperm motility and viability. In the majority of the men with SCI, the sperm count is not abnormal. We elaborate on the effects of the SCI on semen parameters that may contribute to poor motility and poor viability.

Methods: Review.

Design: PubMed and MEDLINE databases were searched using the following key words: spinal cord injuries, fertility, sexual dysfunction, and spermatogenesis. All literature was reviewed by the team of authors according to the various stages of sperm development and transport in the male reproductive cycle.

Findings: The cause of asthenozoospermia appears to be multifactorial.

Conclusion: Current literature does not support the preeminence of a single factor relating to neurogenic reproductive dysfunction in men with SCI. After SCI, there is ample evidence of disturbance of sperm production, maturation and storage, and transport due to an abnormal neuroendocrine milieu. Semen quality seems to be primarily affected by changes to the seminal plasma constituents, type of bladder management, and the neurogenic impairment to the ejaculatory function. Further focused and structured studies are required.

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Key Words: Spinal cord injuries; Infertility, male; Semen quality; Reproductive medicine; Paraplegia; Tetraplegia; Electroejaculation; Vibroejaculation

INTRODUCTION

Spinal cord injury (SCI) is predominantly seen in young men. The average age at injury is 32.6 years (1), and many individuals have not yet started a family. Medical intervention is required to assist the majority of men with SCI to father children. Without medical intervention, infertility secondary to the SCI is virtually universal in men. The devastating effect of SCI on the sexual health of these young men poses a major challenge in both their physical and their psychosocial rehabilitation. For these individuals, treatment of sexual dysfunction is frequently reported to be as important as that of correcting bladder and bowel dysfunction and of greater importance than walking again (2). Furthermore, elucidating the causes of

their infertility might provide valuable clues about other forms of male infertility.

Reproductive dysfunction in men with SCI is the result of combination of erectile dysfunction, ejaculatory failure, and abnormal semen characteristics. Erectile dysfunction in men with SCI is amenable to various treatments (available as either single or combination therapy), including oral treatment with phosphodiesterase-5 inhibitors, intracavernosal injection or intraurethral suppositories of alprostadil, vacuum devices, and penile implants.

Ejaculatory failure in SCI is secondary to autonomic nervous system injury and neuromuscular dysfunction. Various methods were developed to obtain semen from men with SCIs. Cholinesterase inhibitors (neostigmine) were administered intrathecally for the first time by Guttman and Walsh in 1940, resulting in successful pregnancies. However, this method was invasive and could result in a fatal autonomic dysreflexia (3). Subcutaneous physostigmine was used to enhance ejaculation but was abandoned in favor of electrical and vibratory stimulation due to its potential serious cardio-

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Figure 1. The Ferticare vibroejaculator, which is typically used to obtain semen samples from men with spinal cord injury.

vascular side effects (4). With the advent of new assisted ejaculatory methods (eg, vibroejaculation [Figure 1] and electro-ejaculation) and assisted fertilization techniques, the fertility status of men with SCI has now progressed from being practically sterile to potentially fertile.

Cumulative success rates of ejaculation of approximately 86% have been reported using either vibration or electrical stimulation techniques in men with SCI (5). In vibration-induced antegrade ejaculation, the quality was found to be superior to electroejaculated specimens; however, its success rate for patients with injury below T10 remains very poor (6,7). The fertilization rate after electroejaculation is inferior to that achieved via other methods of semen collection (8).

It is well established that the semen quality of men with SCI is poor and that changes are seen as early as 2 weeks after injury (9). The distinguishing character of poor quality is abnormal sperm motility and viability and not the sperm count, which remains comparable to the age-matched population (10,11). The cause of this asthenozoospermia appears to be multifactorial. It does not appear to be related to time since injury, elevated scrotal temperature (especially in the wheel chair-bound population), method of bladder management, or method of ejaculation (12–15). The evidence for frequency of ejaculation as a cause of poor semen quality remains contradictory (16–18). In this paper, we review factors that may contribute to poor semen quality and subfertility in men with SCI.

Testicular Function

Experimental work on acute SCI in rats shows profound effects on the hypothalamic-pituitary-testicular axis by the third day after SCI (19). These changes were

temporary, and a normal hormonal milieu was restored by 14 days. The overall conclusion from animal studies rules out hormonal deficiency as the predominant cause of infertility in SCI. Hypothalamic-pituitary-testicular axis dysfunction has been confirmed in humans after SCI, and its severity has been correlated to the level of injury (20). Testosterone, follicle-stimulating hormone, and leuteinizing hormone levels remained altered for 6 weeks in men with paraplegia and for 4 months in men with tetraplegia. Similar dysfunction was also apparent in the HP-adrenal axis with abnormal cortisol secretion in response to adrenocorticotrophic hormone in men with SCI (21). Overall, 51% of men with SCI have at least one hormonal abnormality and 86% have some hypothalamic-pituitary axis abnormality (22). Hyperprolactinemia is seen very commonly in SCI and might be contributory to testicular hypofunction (23,24). Although abnormal hormonal levels in urine and blood have been reported in many studies in men with SCI, this does not seem to be the primary cause of infertility because equal numbers of studies report normal findings (25–27).

Historically, nearly 65% of men with SCI have abnormal spermatogenesis on testicular biopsy, and the abnormality is generally independent of duration, level, and severity of the injury (27). Testicular interstitial fibrosis and arrest of spermatogenesis have been reported (27,28). Using quantitative micrometric assessment, researchers found that 65% of men with SCI, compared with noninjured fertile controls, had adequate mean spermatid numbers per tubule that met minimum standards for adequate spermatogenesis (29). However, as a group they had significantly decreased numbers per tubule (30). Hirsch et al noted improvements over the decades in testicular biopsies of men with SCI. He hypothesized that the improvements were related to better bladder management over the decades, including an emphasis on low-pressure voiding (31).

Epididymal Function

Epididymal function is sensitive to temperature change (32). Higher temperatures lead to the loss of sperm storage and normal electrolyte transport. Due to the adduction of the thighs and scrotal entrapment associated with prolonged sitting in wheelchairs, elevated scrotal temperatures were found to be associated with a decrease in sperm motility in men with SCI (33,34). Decreasing the scrotal temperature by application of ice packs resulted in overall improvement in motility (27). However, more recently, Brackett et al found no correlation in scrotal temperature and quantitative semen parameters of men with SCI (12). The inconsistencies relating to the findings of the above studies may relate to variations in methodology, such as varying methods of taking scrotal temperatures in men with SCI.

Epididymal function is also sensitive to sympathetic nerve integrity. The human vas deferens is richly supplied with sympathetic adrenergic nerves (35). Sympathetic

stimulation causes movement of sperm from the caudal epididymis to the proximal vas. These peristaltic contractions are elicited by stimulation of hypogastric nerves and by sympathetic neurotransmitters (36,37). Human caudal epididymis and vas also act as sperm stores contributing up to 50% of sperm seen in the ejaculate (38). In rats, the loss of sympathetic innervation causes abnormal accumulation of spermatozoa in the cauda epididymis and also loss of curvilinear and straight-line swimming speed (39,40). More recently, chemical and surgical sympathectomy in rats resulted in delayed epididymal transit but had no effect on fertility using in utero fertilization (41). This suggests that stagnation in the epididymis does not affect sperm quality. In humans, Ohl et al reported that the aspiration of seminal vesicle fluid prior to vibro- or electroejaculation resulted in an improvement in the mean sperm motility. Motility was above that seen in sperm from the aspirated fluid and also above that seen without prior seminal vesicle aspiration (42). This study indicates abnormal transport and storage of sperm in the seminal vesicles of men with SCI. In concordance, Hamid et al reported that repeated vibroejaculation in men with SCI seems to improve the spermatozoa morphology and forward progression, but this finding is not consistent (16).

Seminal Fluid and Changes

After the deposition of semen in the vagina at coitus, the sperm undergoes a process of “capacitation.” This includes a structural change with development of hyper-activated motility and a biochemical change (a process known as acrosome reaction) (43). The direct role of prostatic and seminal vesicle secretions in this process is unknown. However, the antioxidant properties of various molecules in seminal plasma protect the sperm from oxidative damage (44). Fructose from the seminal vesicle provides sperm with an energy source and macromolecules like albumin support and stimulate the sperm (45).

The production of reactive oxygen species (ROS) by human sperm and leucocytes is well known (46). Oxidative effects result in low sperm motility due to rapid loss of intracellular adenosine triphosphate, but oxidative damage to sperm DNA is not always associated with decreased cell viability or motility (47,48). ROS are, however, necessary for regulating the degree of hyper-activation and controlling the sperm activity while undergoing the acrosome reaction (49,50).

In a prospective study of men without SCI, men with high levels of ROS in semen were found to be 7 times less fertile, that is, not capable of spontaneous pregnancy without therapeutic intervention, than men with low ROS (51). Men with SCI seem to have elevated levels of ROS in their semen, which also inversely correlates with their sperm motility (52). This increase in ROS seems to be due to increased oxidative stress due to altered metabolism and leucocytospermia (with resultant increased inflammatory cytokine production) (53,54). The ROS levels

measured were not different in antegrade or retrograde semen samples and were also independent of sample collection method (52). An imbalance between ROS production and scavenging could be a possible contender responsible for male infertility after SCI.

Leucocytospermia is well known in men with SCI, but its significance remains controversial (55). On immunohistochemical analysis, lymphocytes were the most common cells, with T cells being the dominant phenotype (56). It is known that activated T cells secrete cytokines that can prove harmful to the sperm (57). Most of the T cells detected in semen of men with SCI were in the activated form (56), and the associated inflammatory cytokines, such as interleukin-1 β , interleukin-12, and tumor necrosis factor- α , were found elevated in men with SCI (58). Cytokines (eg, interleukin-4 and transforming growth factor- β) were suppressed in SCI, and these are responsible for downregulation of inflammatory responses. Interferon- γ , which is shown to reduce sperm motility and viability, is increased in 67% of the men with SCI (58). Although the rate of semen and urinary infection is very high in the SCI population, semen infection had no effect on sperm counts in these men or pregnancy rates of their partners (14). Treating the urinary tract infection with antibiotics seems to improve sperm counts and pregnancy rates (10% vs 30% with sterile urine).

It has been shown that sperm motility in normal men is inhibited within 5 minutes of contact with seminal plasma of men with SCI. Conversely, seminal plasma from normal men improves the motility of sperm from men with SCI (59). Additionally, the motility of the sperm aspirated from vas deferens of men with SCI was greater than the motility observed in ejaculated samples from these men (60). Although testicular and epididymal factors have a role in poor sperm motility and viability in SCI, the onus seems to have shifted to constituents of seminal plasma. In addition to ROS, a number of constituents have been found to be different in seminal plasma from men with SCI. The concentration of somatostatin in seminal plasma from men who have undergone vasectomy appears significantly higher than in men who have not, suggesting that the synthesis of somatostatin takes place in the sex glands, but its role remains undefined (61). Concentration of seminal plasma somatostatin is low in patients with injuries above T6 (62). Although somatostatin is present in the sperm milieu and its level is altered after SCI, the correlation of low somatostatin levels with altered sperm motility has not been established. After SCI, seminal plasma fructose, albumin, and metabolic enzyme (glutamic oxaloacetic transaminase and alkaline phosphatase) concentrations are all low, whereas chloride concentration is high (63). Derangement in these energy substrates and enzymes suggests deranged sperm intermediary metabolism, which in turn may contribute to asthenospermia. Platelet-activating factor is an important phospholipid mediator stimulating motility, capacitation, and fertiliza-

tion activities of the sperm. Seminal plasma platelet-activating factor acetylhydrolase activity results in depleted platelet-activating factor levels and has been found to be higher in men with SCI with an associated correlation to decreased sperm motility (64). An additional possible causal factor underlying asthenozoospermia is an association between antisperm antibodies and semen from men with SCI. Elevated titers of immunoglobulin G and immunoglobulin A are reported in men with SCI compared with able-bodied infertile men (65). This association between antisperm antibodies and semen from men with SCI is frequent enough to be a possible causal factor underlying the asthenozoospermia (66,67). Changes are also apparent in prostate and seminal vesicle function after SCI (68,69). Prostate-specific antigen is secreted by the prostate and can be used as an indicator of prostate gland activity. Total seminal prostate-specific antigen is decreased in SCI, but serum levels seem unchanged (70). It remains a matter for further investigation to determine how the loss of the balanced function of these accessory sex glands fits in with low fertility potential.

Sperm Ultrastructure

Sperm ultrastructural defects are important factors in abnormal sperm motility and reduced forwards progression (71). Sperm ultrastructure especially the axonemal defects have been studied in men with SCI (72). Axonemal defects and abnormalities of flagella were identified in the majority of patients with SCI, which in addition to defective energy metabolism, formation of ROS, and oxidative stress, appear to add to the sperm malfunction.

Improving Semen Quality

Although there is an abundance of literature regarding the poor quality of semen in SCI, there appears to be a paucity of literature on treatments to improve this quality. Recently, improvement in quality was reported by Cohen et al using monoclonal antibodies against cytokines seen in the semen of men with SCI (73). The results seem promising but were dependent on pretreatment sperm motility rates. Improvement was statistically insignificant in patients with pretreatment sperm motility below 10% or above 30%. Sonksen et al have reported no improvement in semen quality with repeated vibroejaculation, although this does not represent general experience (17,74). In a prospective, controlled study, Hamid et al have shown statistically significant improvement in morphology and forward progression with repeated vibroejaculation over a period of 12 weeks (16).

In infertile men without SCI, high-dose antioxidants (vitamins C and E) had no role in improving the quality and survival of sperm. However, a prolonged abstinence time increased the ejaculate volume, sperm count, sperm concentration, and total number of motile spermatozoa

in this same cohort (75). Zinc therapy improves asthenozoospermia in men without SCI (76). So in theory, if medically approved, in addition to repeated vibroejaculation, zinc supplementation could improve sperm parameters in the SCI population.

Improvement in bladder management, sperm retrieval (by vibro- or electroejaculation and via aspiration from the vas deferens or testes), and testicular biopsy in conjunction with assisted fertilization techniques have played a significant role in indirectly improving fertility rates in the SCI population. In a recently published review, the pooled fertility data revealed a pregnancy rate of 51% and live birth rate of 40%. These data represent fecundity over an unlimited timeline and not cycle fecundity (5). Still, the etiology of poor sperm quality remains unclear.

CONCLUSION

Overall, 51% of men with SCI have at least one hormonal abnormality and 86% have some hypothalamic-pituitary-testicular axis abnormality (21). Despite these abnormal hormonal levels, it does not seem to be the primary cause of infertility in men with SCI, because an equal number of studies report normal results. Males with obstructive azoospermia have similar quantitative parameters of spermatogenesis as that seen in men with SCI, pointing to a postspermatogenic cause for neurogenic infertility. Epididymal function appears sensitive to temperature change and also sensitive to sympathetic nerve integrity; however, there appears to be no correlation between scrotal temperature and quantitative semen parameters of men with SCI.

Maintenance of sperm function requires normal secretions from prostate and seminal vesicles. Dysfunction at this level might result in subfertility. The balance between ROS production and scavenging in men with SCI appears abnormal and may be responsible for infertility. Men with SCI have elevated levels of ROS in their semen. This increase in ROS seems to be at least in part due to an increased oxidative stress and leucospermia. There is a correlation between the percentage of patients with normal spermatogenesis and the improvement in bladder management and infection control (31). Semen infection appears to have no effect on sperm count or pregnancy rates. The responsibility for poor sperm motility and viability in SCI seems to have shifted towards the constituents of the seminal plasma.

Autonomic nervous dysfunction seems to affect movement of sperm from the caudal epididymis and proximal vas. Although this may not affect the intrinsic motility of the sperm, it may have an impact on final mature movements. In addition, there is considerable neurogenic impairment to the ejaculation process that requires assisted ejaculation techniques.

The definitive causal mechanism leading to abnormal semen quality in men with SCI remains to be elucidated.

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