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Clinical Case of the Month

Treatment of infertility

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Introduction

The ability to ejaculate and semen quality is severely impaired in the majority of men with spinal cord injury (SCI) and, consequently, pregnancies caused by SCI men without medical intervention are rare.[1–3] The most common methods to induce ejaculation in SCI men are penile vibratory stimulation (PVS)[4–7] and electroejaculation (EEJ).[8–11]

In this case, we present a common fertility treatment situation with an SCI man and his wife.

Case presentation

A 32-year-old C5 incomplete tetraplegic man and his 35-year-old wife seeking treatment for infertility were admitted to our clinic. Before the spinal cord injury 4 years previously, he had normal ejaculatory function. After the injury it was not possible to obtain ejaculation by sexual stimulation or masturbation. Serum hormonal analyses of follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol and testosterone were within normal limits. Orchiodometry revealed normal testicular size on both sides. PVS was then performed with a new medical grade vibrator (Figure 1) which has been developed for this purpose. A vibratory amplitude of 2.5 mm and a frequency of 100 Hz was used as previously described.[4] The center of the vibrator knob was applied to the preputial frenulum and held in the same position until antegrade ejaculation occurred after 40 s of stimulation. The ejaculate was collected in a non-spermicidal container. Due to the potential risk of autonomic dysreflexia the blood pressure was monitored during the procedure and no significant increase in the blood pressure was seen. A diagnostic raw semen analysis of the antegrade ejaculate was performed immediately following the procedure and showed a volume of 3.4 ml and a sperm concentration of 404 million per ml with a motility rate of 27%. The percentage of sperm with normal morphology was 62%.

The couple entered a home fertility programme of PVS combined with vaginal self-insemination. They were carefully instructed at the outpatient clinic to perform PVS by themselves. The time of ovulation was identified by monitoring basal body temperature. The ejaculate was collected by the partner into a non-spermicidal container. A 10 ml syringe was then used to instill the ejaculate intravaginally. No pregnancy occurred following eight cycles of home insemination.

Intrauterine insemination (IUI) was then performed. Prior to IUI the wife was thoroughly evaluated by hystero-salpingography and assessment of ovulation and found normal. Before insemination by IUI, clomiphene citrate (Pergotime) was used in a dose of 100 mg per day on days 3–7. Vaginal ultrasound examination was used for ovulation timing. When the leading follicle reached 18 mm in diameter, human chorionic gonadotropin (hCG, Profasi) 5000 IU was administered subcutaneously to induce ovulation. Intrauterine insemination was then performed 38 h following the hCG-injection. No pregnancies were achieved during a total of six cycles of IUI. Before IUI the semen obtained by PVS was processed by the Percoll-technique and the total number of motile sperm used for the IUI cycles ranged from 30–200 million (median 85).

The couple was then offered in-vitro insemination (IVF). Prior to IVF the female partner was treated with a gonadotropin releasing hormone analogue (GnRH, buserelin, Suprefact) followed by stimulation with human menopausal gonadotropins (Humegon) according to a long protocol. Human chorionic gonadotropin was given 36 h before oocyte aspiration and a maximum of two embryos were transferred into the uterine cavity 48 h following the oocyte aspiration. A total of four IVF cycles were performed. All cycles resulted in fertilization with a cleavage rate of 80%

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Figure 1 Ferti care® personal (Multicept, Rungsted, Denmark) vibrator developed to induce ejaculation in men with spinal cord injuries. The amplitude and frequency may be set at the recommended 2.5 mm and 100 Hz, or according to individual requirements. The options available include amplitudes between 1.0 – 3.5 mm and frequencies between 70 – 110 Hz

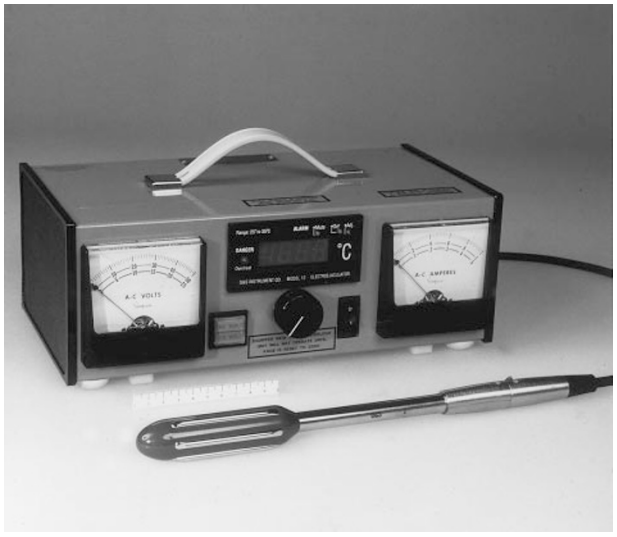

Figure 2 Seager Model 11 Electroejaculator and rectal probe (Dalzall USA Medical Systems, The Plains, VA, USA). The rectal probes used during the electroejaculation procedure are generally 3 cm in diameter with either a transverse or a longitudinal arrangement of the electrodes. Alternating current (0 – 50 V/0 – 1000 mA) is used to perform the electrical stimulaton

(median number of oocytes aspirated per cycle was ten, range 5 – 14). A singleton pregnancy (still ongoing) was achieved after the fourth attempt of IVF. Following Percoll-technique, the total number of motile sperm used for the IVF cycles ranged from 28 – 180 million (median 112).

Comments by Dr Ohl

This case presentation represents a very common situation we see at the University of Michigan. Many of my comments regarding management are based on our program's experience in EEJ but I believe the comments are valid since similar sperm problems are seen in both EEJ and PVS.

The initial evaluation of this patient and his spouse prior to the initial PVS was correct. It was a limited evaluation. Unfortunately, many men with SCI seeking infertility treatment at our center have already undergone extensive unnecessary evaluation, sometimes including invasive procedures such as testicular biopsy and vasogram. Spinal cord injured men should be treated the same as any man with an infertility problem – a 'sperm count' should be obtained prior to invasive testing. Therefore, history, physical exam and hormonal assays are all that should be performed prior to proceeding with ejaculation induction.

The next question to consider is which type of ejaculation procedure to perform – EEJ or PVS. Electroejaculation is clearly a more reliable procedure. Virtually 100% of SCI men ejaculate with EEJ *versus* 60% to 80% with PVS. Dr Sønksen, the lead discussant of this case, should be congratulated for determining the importance of the vibratory amplitude and increasing PVS ejaculation rates to this range.[4] It is because of his work that we have seen success with PVS and in recent years shifted our emphasis to PVS as our primary procedure .

Despite the fact that PVS works in a smaller percentage of the cases, it should always be tried first. Patient acceptance is substantially higher for PVS over EEJ and there is a suggestion of better sperm quality and function with PVS as well.[12] Electroejaculation is reserved for PVS failures. In the very rare event that EEJ and PVS both fail to cause seminal emission, surgical extraction of sperm can be considered, and I believe that ejaculation induction failure is the only acceptable reason for surgical sperm extraction in the SCI population. Once adequate sperm quality is demonstrated, attempts at pregnancy can then proceed.

While I am not totally adverse to home insemination, I believe that success with this procedure will be extremely low, for two main reasons. The first is related to the insemination route. We have reported on functional abnormalities of the sperm obtained by EEJ[13] and these functional abnormalities have also been verified in men undergoing PVS. These defects include poor survival in incubation and cervical mucus transport. Home insemination success requires that these fragile sperm survive the hostile vaginal

environment and also traverse the cervical mucus to get into the uterus, tasks that the functional abnormalities may not allow. In the University of Michigan program, multiple initial attempts of physician-performed vaginal inseminations resulted in no pregnancies. With intrauterine delivery of sperm, the pregnancy rate immediately rose to greater than 30% per couple.

Secondly, I believe that patient-directed home ovulation timing is suboptional. In this couple, basal body temperature charting was the primary method used. Since SCI sperm also has decreased motility longevity,[14] ovulation timing is of the utmost importance. The delivery of sperm should be performed as close to the time of ovulation as possible, or even after the time of ovulation. Urine luteinizing hormone detection kits may improve home ovulation timing.

Intrauterine insemination is the initial procedure used in our hospital. In the case history, more extensive monitoring and accurate timing of ovulation was seen. Since IUI was coordinated with hCG injection, the delivery of sperm at the time of ovulation was more reliable. The use of clomiphene citrate is optional, as we have not seen an increase in pregnancy rate with the use of this drug. Even though our success rate of 34% per couple by EEJ/IUI is significant, one must realize that this implies a 66% failure rate.[15] I believe that low IUI success rate is related to the sperm functional defects and remaining uncertanties about ovulation timing with IUI. We currently recommend between 3–6 cycles of IUI before proceeding onto higher levels of reproductive techniques.

By advancing to IVF, this couple's best chance of pregnancy is seen. In failures of IUI, our pregnancy rate in one attempt of IVF was 37%.[15] This clearly demonstrates that IVF is superior in attempting to achieve pregnancy with EEJ sperm. We do not go directly to IVF because of a reasonable success rate with IUI alone and because of the high cost of IVF to patients in the United States, since most insurance plans do not cover expenses related to assisted reproductive technologies.

The high fertilization rate in the case history is not surprising. Most SCI men are able to fertilize oocytes in-vitro, despite multiple failures of IUI. Despite the high fertilization rates, however, this couple did not become pregnant until the fourth cycle of IVF. This may be related to transfer of only two embryos per cycle. Transferring two embryos, while decreasing the rate of multiple births, will also decrease the pregnancy rate. In the United States, where government control of IVF is less specific than in Denmark, we would generally transfer four embryos per cycle. With this philosophy, we have enjoyed a significant IVF pregnancy rate (37%), while maintaining a multiple birth rate of only 18% including only one triplet pregnancy. In my opinion, this record seems to represent a good compromise between the problems associated with multiple births and disappointment of multiple failures of IVF.

Comments by Dr Momose

Two difficulties must be overcome by SCI men who desire to father their own children; one is to obtain semen and the other is successful insemination. The most common procedures used to obtain semen are PVS or EEJ. In general, PVS should be preferred as the first choice for SCI men as it is less invasive and the efficiency of over 75% is equal to EEJ. The presented case, a C5 incomplete tetraplegic man, is likely to be burdened with neurogenic bladder dysfunction of upper motor neuron lesion type, and incomplete damage to sensory neurons and will probably endure pain during electrostimulation and require general anaesthesia. Consequently, PVS is considered the better first choice.

The results of semen analyses indicated low sperm motility rate (27%) in contrast to relatively good volume and concentration that is consistent with the results reported in the literature.[16] The couple performed eight cycles of vaginal self-insemination and six cycles of IUI, none of which resulted in pregnancy. In principle, we consider the sperm motility rate of a good candidate for artificial insemination to be higher than 50%. In our past experience of artificial insemination with more generous indication, the rate of achieved pregnancy was 2.5% where the mean sperm motility rate of the husbands was 10%. In case of IUI failure, the next choice is IVF as in the presented case. Our criteria for IVF candidates include a sperm motility rate higher than 20%, which the presented case meets.

The current final step that is clinically available is intracytoplasmic sperm injection (ICSI). This technique requires only 5–10 motile spermatozoa in total to achieve pregnancy. We have two successful cases as yet, in one of which the sperm motility rate was almost 0% and in the other 5%.[17] Theoretically, employment of ICSI almost always enables fertilization followed by pregnancy, even if the semen contains only a few spermatozoa as is the case in some patients. The development of reproductive technologies has decreased the significance of semen quality. Although reproductive medicine in SCI men has achieved remarkable progress both concerning assisted ejaculation and fertilization, it should be noted that selection of the treatment must be made according to the ethical basis of the couple. The technique with the highest efficiency is not the best way for all couples.

Comments by Dr Rocha and Dr Barros

This patient was probably a fertile man before trauma as he has normal testes size and hormone levels. Almost all of male SCI patients experience fertility problems related to erectile and/or ejaculatory dysfunction as well as poor semen quality. Erectile and

ejaculatory problems are caused by the neurologic lesion. The poor semen quality may originate from the neurologic lesion as well as from the high levels of free radicals in the ejaculate.[18] Consequently, only 1% of these patients are able to generate pregnancies by sexual intercourse.[19] When treating infertility problems in SCI patients we should take into account not only the problems related to the trauma but also problems related to the partner, especially the woman's age.

Ninety per cent of these patients require assisted ejaculation.[20] The author's choice to use PVS to obtain ejaculation is the most adequate due to its simplicity and because this technique works very well in patients with lesions above T10 with an intact lower sacral cord.[21] Special caution must be taken with dysreflexia as well as penile skin lesions. If the patient has an associated lower cord lesion or if the vibratory technique is unsuccessful another option would be EEJ with a rectal probe. This method procures semen in two thirds of patients in whom PVS fails.[22]

The second problem of SCI patients is the semen quality. The number of sperm with low motility exhibited by this patient is in accordance with the literature. According to Le Chapelain *et al*[23] the mean semen volume procured by PVS is greater than that obtained using EEJ and the percentage of motile sperm was significantly lower in semen procured by EEJ as opposed to that collected by PVS. In the present case we would not try vibratory ejaculation plus vaginal injection of the semen because the success rate of this method is very low and the patient's partner is not so young, demanding a quick solution. Intrauterine insemination plus hCG stimulation to induce ovulation monitored by ultrasound would have been our first choice. The method has a pregnancy chance of 10% to 20% and represents an easy and cheap method.[24] However, in order to save time we would have tried this method for just two to three cycles. If the method did not work, our next step would be IVF for four cycles. If pregnancy were not obtained using IVF we would go directly to ICSI. Although there are only a few series reported in the literature using assisted fertilization in SCI patients, the cumulative pregnancy rates after eight cycles of IUI and three cycles of IVF are about 30% per cycle and 70% per cycle, respectively.[25] The adoption of this more aggressive approach is justified by the age of the partner. After 35 years of age women's fertility decreases and this couple's chance to achieve a pregnancy will decrease with time.

Discussion

In general, all authors agree that PVS should be the first choice of treatment in SCI men with ejaculatory dysfunction and spinal cord lesions above T10.

Vibratory stimulation of the penis to obtain ejaculation was first described by Sobrero *et al*[26] in a group of non-spinal cord impaired men. The first reported use in an SCI man was with a hand massager.[27] It is largely due to Brindley[5] that the use of PVS in SCI men has become widespread.

The vibratory amplitude is of great importance when inducing ejaculation by PVS. In a recent study detailed measurements of the vibratory output demonstrated that a vibratory amplitude of 2.5 mm at a frequency of 100 Hz produced significantly higher ejaculation rates (96%) compared to much lower ejaculation rates (32%) with an amplitude of 1 mm.[4] This indicates that a high amplitude vibration is essential to exceed an ejaculatory threshold to activate the ejaculatory reflex in the majority of SCI men. In a study by Ohl *et al*[28] 65% of 34 SCI men obtained antegrade ejaculation when using a 2.5 mm vibratory amplitude at 100 Hz, but the ejaculation rate was 81% in men with spinal cord lesions above the T10-level.

A vibrator (Figure 1) which meets the required frequency of 100 Hz and an amplitude of 2.5 mm[4] has been developed for clinical as well as home use.

Men who are anejaculatory from lower motor neuron lesions will not respond to PVS but usually to EEJ. Electroejaculation was first described in 1931 in humans by Learmonth.[29] The first rectal probe EEJ was performed in a group of SCI men in 1948 by Horne *et al*.[30] We currently use the EEJ equipment developed by Professor Seager (Figure 2). The probe is inserted transrectally and the electrodes are placed in contact with the rectal mucosa in the area of the prostate gland and the seminal vesicles. The electrical stimulation is given with progressively increasing voltage until ejaculation is completed. The fraction of antegrade ejaculate does not occur as a projectile ejaculation, but rather as an intermittent release of semen during the course of the procedure. Prior to the EEJ procedure, the patient is catheterized to completely empty all the urine, since many individuals have a substantial portion of the ejaculate going into the urinary bladder (retrograde ejaculation). Because urine may adversely effect this retrograde ejaculate a sperm friendly medium (eg Ham's F 10 medium) can be instilled into the bladder before the EEJ. After the procedure the bladder is then catheterized to empty the retrograde fraction. It should be noted that individuals with sensation will require either a spinal or general anaesthetic before treatment.

The mechanism by which EEJ operates is not clear but direct electrical stimulation of the smooth muscles of the *vas deferens*[31] as well as local muscle stimulation[32] and stimulation of the myelinated efferent nerves close to the rectum[33] has been suggested as the mechanism of action. However, it remains clear that ejaculation can be induced in nearly 100% of SCI men undergoing the procedure.[9,34]

Despite the fact that ejaculation can be induced in nearly all SCI men by PVS and EEJ, the semen is of poor quality.[9,28,35–38] In general, the total number of sperm is within normal range but the motility is low compared to World Health Organization Standards.[39] The reason for the poor semen quality in SCI men remains unknown but several factors have

been suggested to explain this problem including recurrent urinary tract infections, type of bladder management, stasis of prostatic fluid, testicular hyperthermia, abnormal testicular histology, changes in the hypothalamic-pituitary-testicular axis, sperm antibodies, and long-term use of various medications.[40]

The literature is unclear whether the quality of semen originating from PVS is superior to sperm from EEJ in SCI men.[3] Recently, in a study by Ohl *et al*[12] it was demonstrated that antegrade ejaculates from PVS compared to EEJ in the same SCI men had a significantly higher sperm motility (26% *versus* 11%), viability (25% *versus* 10%) and total motile sperm count (185 millions *versus* 97 millions). Furthermore, this study also reported that the hamster egg penetration by SCI sperm is superior with PVS (54%) compared to EEJ (22%). However, when adding the number of sperm isolated from the urine (retrograde fraction) after both procedures, only a slight advantage in the sperm quality from PVS was seen. Two other recent studies[23,41] demonstrated that the motility rate was significantly better in total ejaculates (antegrade + retrograde ejaculations) from PVS compared to EEJ. Whether the difference in sperm motility and viability between PVS and EEJ may have any influence on the reproduction capability will have to be evaluated in a randomized prospective study including SCI men and their partners undergoing fertility treatment.

PVS and vaginal self-insemination performed by the couple at home is an option for those SCI men with an adequate semen quality.[35–37,42,43] In 1984 Brindley[35] reported seven home pregnancies following PVS and vaginal self-insemination with delivery of five healthy babies (one ongoing/one spontaneous abortion). Recently, several pregnancies have been reported from PVS procedures combined with self-insemination at home as shown in Table 1. Most studies reported that multiple ovulation cycles were used to achieve the home pregnancies. The ovulation timing as stated in the comments by Dr Ohl is of the utmost importance and the use of luteinizing hormone detection kits should be further evaluated to determine whether they may improve home pregnancy rates. The age of the female partner in this case presentation and the low pregnancy rate of vaginal insemination at home leads Dr Rocha and Dr Barros to recommend the fertility treatment is initiated with IUI. In general, the fertility of females will decrease after 35 years of age and this should be considered before initiating a home program of PVS and home insemination. However, Table 1 shows that pregnancy rates (25% to 62%) after multiple cycles of home PVS and insemination is reasonably good. At the present time, it seems reasonable to offer motivated young couples with an adequate semen quality the inexpensive possibility of PVS combined with home-insemination as a firstline option.

The use of assisted reproductive techniques combined with PVS and EEJ may increase the possibility of achieving pregnancy in the partners of SCI men. Recently, several successful pregnancies have been reported[15,25,36,37,42–45] using sperm obtained by PVS or EEJ combined with assisted

Table 1 Pregnancy results in spinal cord injured men and their partners using penile vibratory stimulation and vaginal self-insemination at home

References	*Number of couples attempting procreation*	*Number (%) of couples with pregnancy*
Dahlberg *et al* 1995 (36)	19	8 (42%)
Nehra *et al* 1996 (37)	8	5 (62%)
Sønksen *et al* 1997 (42)	16	4 (25%)
Löchner-Ernst *et al* 1997 (43)	54*	22 (41%)

*Not stated in the article, personal communication

Table 2 Pregnancy results from selected studies in spinal cord injured men and their partners using penile vibratory stimulation (PVS) and electroejaculation (EEJ) combined with intrauterine insemination (IUI) or *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI)

References	*Ejaculation method*	*Reproductive technique*	*Number of couples attempting procreation*	*Number (%) of couples achieving pregnancy*
Dahlberg *et al* 1995 (36)	PVS/EEJ	IUI/IVF	19	11 (58%)
Ohl *et al* 1995 (15)	EEJ	IUI/IVF	120	54 (45%)
Brackett *et al* 1995 (25)	PVS/EEJ	IUI/IVF	23	11 (48%)
Nehra *et al* 1996 (37)	PVS/EEJ	IUI/IVF	31	12 (39%)
Sønksen *et al* 1997 (42)	PVS/EEJ	IUI/IVF/ICSI	12	6 (50%)
Löchner-Ernst *et al* 1997 (43)	PVS/EEJ	IUI/IVF/ICSI	82	37 (45%)
Hultling *et al* 1997 (44)	PVS/EEJ	IVF/ICSI	25	16 (64%)
Brinsden *et al* 1997 (45)	EEJ	IVF	35	18 (51%)

reproductive techniques such as IUI or IVF with or without ICSI (Table 2). The overall pregnancy rate per cycle from those studies[15,25,36,37,42–45] is about 25%. It should be noted that this rate is similar to the pregnancy rate per cycle during natural procreation in healthy couples who want to become pregnant (25% to 30%),[46] although assisted ejaculation and reproductive techniques are required in SCI men and their partners.

As discussed in this paper several fertility treatment options are available to enhance the reproduction prospects in SCI men and their partners. The proper choice of treatment should be made through coordinated efforts of different specialities including urology, gynaecology and rehabilitation. As mentioned by Dr Momose, the most effective reproduction technique may not be the best treatment for all couples. Therefore, when proceeding onto higher levels of reproductive techniques, it is also of importance to inform the couples about possible side-effects from hormonal ovulation induction as well as problems related to multiple births, and finally the couples' own ethical considerations must be taken into account.

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