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Sexuality and Reproductive Health Following Spinal Cord Injury

Summary

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Introduction

Spinal cord injury (SCI) is most often the result of a trauma to the spinal cord, but can also be associated with congenital or degenerative disease. In the United States alone currently there are approximately a quarter million people with SCI. Every year, approximately 10,000 people in the United States survive an acute traumatic injury to the spinal cord. The majority of these people are male and under the age of 25.[1] In addition to paralysis, persons with SCI will likely experience problems with bladder and bowel control, as well as alterations in sexual functioning.[1,2-4] The impact of a SCI on sexual functioning depends on the degree of the injury and its location on the spinal cord.[5,6] Sexual dysfunction in persons with SCI may have both physiologic and psychological (e.g., body image, self esteem) elements that can be distressing regardless of the person's gender, age, or culture.

Both men and women report a decreased desire for sexual activity following their injury.[7,8] Frequency of sexual activity is also known to decrease after injury in both men and women.[7,8] In men with SCI, factors affecting sexuality typically include erectile and ejaculatory dysfunction.[9-11] Factors affecting women with SCI may include difficulties having comfortable intercourse, and the ability to reach or feel orgasm.[5,12,13]

Although some men with SCI are unable to have erections, many still maintain the ability to have some erectile function, albeit of insufficient quality and duration for intercourse.[14] Possible treatments include devices such as the vacuum erection device as well as the injection of vasoactive drugs into the penis.[15,16] A recent innovation to improve erectile function in men with SCI has been the approval of the drugs such as sildenafil (Viagra®). Infertility is an issue for men with SCI[14,17,18] more than with women. Male infertility results from the combination of ejaculatory dysfunction and abnormal sperm quantity and quality. Techniques to remediate erectile dysfunction and ejaculation have vastly improved the fertility potential of men with SCI.[19-23] Stimulation to obtain ejaculate for insemination of a partner is now routinely performed. Usually, ejaculate is obtained through the use of penile vibratory stimulation or electroejaculation, but other techniques to treat SCI-related male infertility are myriad.

Health care providers have become increasingly aware of the importance of sexuality in the rehabilitation process.[22,23] Current approaches to "best practices" concerning the topic of sexuality and reproductive health in persons with SCI are opinion-based, typically generated by clinical experience with small patient populations in select hospitals and rehabilitation facilities. The Consortium for Spinal Cord Medicine (sponsored by the Paralyzed Veterans of America) has identified the issue of sexuality and reproductive health to be a high priority topic for improving the quality of life for persons with SCI.

Last year, at the request of the Consortium for Spinal Cord Medicine, the Agency for Healthcare Research and Quality (AHRQ) commissioned the University of Ottawa's Evidence-based Practice

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Evidence-Based Practice

Center (UO-EPC) to conduct a feasibility study to determine if there is sufficient credible literature to support a comprehensive systematic review on the topic of "Sexuality and Reproductive Health Following SCI." In this feasibility report a reasonably large body of evidence was identified examining different aspects of sexuality and reproductive health following SCI. In general, these studies are of a lower level of evidence and open to several sources of bias. Therefore, AHRQ requested a comprehensive evidence report that incorporates and builds on findings from the UO-EPC phase I feasibility study.

Key Questions

As a result of findings from the phase I feasibility study, this report focuses on two questions and their sub-questions. Question 1 focuses on issues related to fertility, pregnancy rates, and live births in persons with SCI. Question 2 focuses on issues related to male impotence post SCI.

1. Reproductive health: What is the current fertility rate for men and women after SCI?
   - Are fertility rates changed by freezing a new patient's sperm?
   - Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?
   - To improve fertility rates, when should invasive techniques such as testicular biopsy or aspiration or intracytoplasmic sperm injection (ICSI) be pursued?
   - Are there pregnancy complications and prospective obstetric management issues for SCI females?
2. Male sexuality: How has the availability of Viagra® and other remediation affected sexual function, frequency of activity, and adjustment after SCI?
   - Is Viagra® really more benign than intracavernous injections?
   - How does the morbidity of prostaglandin injections compare to the older (less expensive) papaverine?
   - What is the morbidity of vacuum tumescence devices?
   - What indications, if any, remain for implantable penile prosthetic devices?

Methods

A Technical Expert Panel (TEP) consisting of six members was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

Building on a preliminary search strategy conducted by UO-EPC in the feasibility task order, a comprehensive updated search for citations was conducted using six databases (MEDLINE®, PreMEDLINE®, CINAHL®, Cochrane Central Register of Controlled Trials, SocioFile, and PsycINFO). Following the suggestions of the TEP, additional published literature was sought through searches of relevant associations' proceedings for the years 1997-2002. In addition, industry was contacted for ongoing and/or unpublished data. A final set of 2,128 unique references was identified and posted to the UO-EPC's Internet-based software system for review.

Eligibility Criteria

Studies were considered relevant if they described both male and/or female (adult or adolescent) populations with SCI, involved any type of study design; published or unpublished, and reported in English. Studies were also eligible for inclusion if each met predetermined criteria. In reproductive health, design criteria consisted of whether the study discussed a fertility intervention; included a pre and post intervention for fertility rates; contained an original report of a measure of fertility rates in males, females, or both; or whether it reported an original intervention trial after SCI. Eligible interventions included physical, surgical, laboratory techniques, or prescription medications. Eligible fertility outcomes included pregnancies, live birth rates, sperm motility, successful sperm harvesting, ejaculations, sperm count, percent viable sperm, hormonal, ovulation rates, cycle function, other measures of sperm morphology, and volume of ejaculation.

In male sexuality, design criteria consisted of whether the study reported an original intervention trial or series with a pre and post measure for sexual dysfunction after SCI, contained an original report of a measure of sexual dysfunction, or whether the article discussed an intervention for sexual dysfunction. Eligible interventions included cognitive/behavioral, prescription medications, and surgical or hormonal interventions. Eligible outcomes included psychological outcomes (e.g., validated sexual function questionnaire for males and/or females, structured interviews with qualitative analysis, educational component, global efficiency, or patient logs), and/or physiologic outcomes (e.g., penile and/or clitoral engorgement, endocrine, ultrasound testing of testicular size).

As an extension of the phase I feasibility study, two reviewers were employed at the relevance assessment phase of the evidence review. Two levels of screening for relevance were used, with the first level directed at bibliographic records during

phase I, the feasibility study (i.e., title, authors, key words, abstract), and the second level focused on those "full report" articles retrieved based on the results of the first level of screening. Screenings for relevance, assessments of study quality, and data abstraction were completed using the UO-EPC's review management Internet-based software, which resides on a secure Web site.

Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[24] Reports were not masked given the equivocal evidence regarding the benefits of this practice.[25,26] Disagreements were resolved by forced consensus and, if necessary, by a third party.

Data Abstraction

Following a calibration exercise, two reviewers independently abstracted the contents of each included study using an electronic data abstraction form developed especially for this review. Once reviewers completed their work, all work was checked by their counterparts. Data abstracted included the characteristics of the following: report (e.g., publication status, language of publication, year of publication); study (e.g., sample size, research design, number of arms); population (e.g., age, percent males, diagnosis description); intervention/exposure (e.g., Viagra® for sexual function, testicular biopsy for fertility rates); and withdrawals and dropouts.

Study Quality

In this report, study quality was assessed through examination of each individual report rated independently by two assessors. Quality was defined as the confidence that the study's design, conduct, analysis, and presentation has minimized or avoided biases in any comparisons.[27] Several approaches exist to assess quality: components, checklists, and scales. Therefore, a combination of methods was used in an effort to ascertain a measure of reported quality across different study designs.

For RCTs the Jadad scale was used. This is a validated scale consisting of three items that assesses the methods used to generate random assignments, double blinding, and a description of dropouts and withdrawals by intervention group.[28] The scoring ranges from one to five, with higher scoring indicating higher quality. In addition, allocation concealment (i.e., keeping the randomization blind until the point of allocating participants to an intervention group) was assessed as adequate, inadequate, or unclear.[29] An *a priori* threshold scheme was used for sensitivity analysis: a Jadad total score of ≤ 2 indicates low quality with scores > 2 indicating higher quality.

Cohort and case-control study reports were assessed using the Newcastle-Ottawa scale (NOS).[30] The NOS is an ongoing collaboration between the Universities of Newcastle, Australia, and Ottawa, Canada. It was developed to assess the quality of nonrandomized studies with its design, content, and ease-of-use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results.

Qualitative Data Synthesis

A qualitative synthesis was completed for all studies included in the evidence report. A description is provided of the progress of each citation through the review process, and includes information pertaining to each report, such as their sample size. The qualitative synthesis was performed on a question-specific basis, with studies grouped according to research design (e.g., RCTs, observational studies). Each synthesis includes a narrative summary of the key defining features of the study report, if stated, (e.g., a priori description of inclusion/exclusion criteria), population (e.g., diagnosis-related), intervention/exposure (e.g., use of Viagra®), outcomes, study quality, applicability, and individual study results. A brief study-by-study overview typically precedes a qualitative synthesis.

Quantitative Data Synthesis

For several of the questions investigated in this evidence report, quantitative data synthesis was deemed appropriate. However, most of the studies were non-comparative case series and outcomes were in the form of single proportions (e.g., proportion of couples achieving at least one pregnancy). Current meta-analytic methodology generally focuses on data from studies that include a control group, such as randomized controlled trials. From a meta-analytic perspective, one of the strengths of studies that include control groups is that even if there is some degree of heterogeneity in characteristics such as population or intervention across studies, there may be little statistical heterogeneity in the contrast between outcomes in the treatment and control groups across studies. This protection against heterogeneity is not available in studies without a control group. Judicious selection of comparable studies for inclusion in a meta-analysis of single proportions therefore becomes especially crucial. In the present work, heterogeneity of single proportions was assessed using Pearson's chi-square test. P-values less than 0.10 were taken to indicate statistically significant heterogeneity. Forest plots were constructed using Wilson score confidence intervals around individual study proportions.[31] Pooled estimates and their confidence intervals were obtained using the random effects estimator of Laird and Mosteller.[32]

Results and Discussion

Literature Search

A total of 2,420 bibliographic records were retrieved through database searches. After duplicate records were removed, 2,082 unique items remained. An additional 46 potentially relevant studies were identified through conference abstracts or were nominated by manufacturers. Therefore, a total of 2,128 reports were evaluated against the eligibility criteria and after the initial screening for relevance, 1,627 records were excluded. Although the majority of the initial screening was performed in the phase I feasibility study, the additional studies that were identified when the search was "rerun" at the beginning of this study (n = 98, of which 47 were duplicates) were screened according to phase I criteria. The reasons for exclusion were: not relevant to SCI (n = 530); not relevant to sexuality or reproductive health (n = 410); case report or opinion piece (n = 282); no relevant measure reported (n = 271); not relevant to any of the questions (n = 78); and, report pertaining to adolescent or child only (n = 6). The remaining 501 reports were then retrieved and subjected to a more detailed relevance assessment. Two hundred and forty-five of these reports dealt with issues relating to fertility and 289 of the reports examined sexual dysfunction. After further relevance assessment, 180 of the 246 reports on fertility and 232 of the 289 reports on sexual dysfunction failed to meet the inclusion criteria of phase II. In total, 122 reports were deemed relevant for the systematic review—66 of the reports examined fertility and 56 reports examined sexual dysfunction in individuals with SCI.

Study Results

The 122 studies included 6,668 individuals, ranging in age from 16 years to 81 years, of which 78 percent of the studies enrolled only men, with 6 percent reporting all female participation.* As might be expected, the complete spectrum of SCI severity was included across the studies. Eighty-seven studies (71 percent) reported on the level of lesion, however, only 18 (15 percent) reported on American Spinal Injury Association level. However, final classifications of data on severity of SCI injuries are complicated in this review due to inconsistencies in the reporting of severity of injury. The majority of studies included in this review used a non-comparative study design (61 percent) to address the question under consideration. For example, a group of males might be given a specific intervention to improve ejaculation rates. Typically, the authors did not select a comparator group and only reported specific outcomes on this group. Few RCTs exist to evaluate the efficacy of male sexual dysfunction and the majority of those are duplicate publications, perhaps giving the impression of being more broadly evaluated than one might think on first impressions. The quality of reporting of the 122 studies included here is less than optimal. For example, of the 75 non-comparative studies, none of them reported on all the quality items we used to evaluate their reports. The highest number of quality criteria met was 16/19 items, and this was achieved by only one (1 percent) of the 75 studies.[33]

Question 1. What is the current fertility rate for men and women after SCI?

Fertility in females after SCI

There were no studies found that investigated this question.

Fertility in males after SCI

Ejaculation rates. Different aspects of male infertility have been studied. Reports in the literature on this topic can be grouped, and some information pooled. Much of the earlier work in this area centers on interventions to aid males with SCI to ejaculate, either during sexual activities with their partners or in a clinic situation to harvest semen for implantation. Different authors and clinics have chosen different methodologies to aid ejaculation in males with SCI. They include intrathecal or subcutaneous physostigmine with masturbation, penile vibration techniques with or without pharmacologic enhancement, or electroejaculation.

Ejaculation rates results from 22 studies that used vibration and/or electrode stimulation in males with SCI. Overall, these interventions resulted in an overall ejaculation response rate of 86 percent (random effects pooled estimate: 0.86, 95% C.I. 0.80, 0.93). When data from studies examining vibration and/or electrode stimulation to provoke ejaculation are pooled, a large degree of heterogeneity is observed. This observation reflects the inclusion of early studies that were aimed at establishing optimal parameters for the technique (e.g., vibration amplitude, electricity parameters), as well as the inclusion of more recent studies which implemented the now common practice of first starting with vibration and later including electroejaculation to increase success rates.

Pregnancies and live births. Not all authors chose to present both pregnancy and live birth data. However, there is no suggestion in the literature that the spontaneous abortion rate of a pregnancy conceived from an SCI male exceeds that of the general population; therefore, we chose to combine both sets of data. These results represent the number of couples who have achieved at least one pregnancy or live birth over the number of couples who tried to conceive. It is very important to note that some authors reported their fertility rates after very simple

* "Couples" were counted as a single case pertaining to number of participants enrolled. Fourteen percent of the included studies reported on the enrollment of couples only or couples together with single-case male participants

procedures such as vibration or electrode ejaculation, whereas some studies were performed in clinics that greatly increased the odds of achieving pregnancy by adding a variety of advanced fertility techniques. Data from the 17 studies documenting pregnancy rates were pooled and indicate pregnancy rates of 51 percent (random effects pooled estimate: 0.51, 95% C.I. 0.42, 0.60). Data from the 13 studies documenting live-birth rates were pooled and indicate live birth rates of 40 percent (random effects pooled estimate: 0.40, 95% C.I. 0.33, 0.48). The heterogeneity of these pooled results is explained by the addition of advanced fertility techniques that increase the success rates for these endeavors by up to four times, compared with insemination alone.

Are fertility rates changed after freezing a new patient's sperm?

There is little data to support the practice of freezing the sperm of SCI males after 16 days post-injury, and that even the advantages of early freezing (within the first 2 weeks) is outweighed by the loss of sperm motility during the procedure, since with modern techniques one is virtually certain of obtaining fresh sperm from the SCI male when he is ready to conceive a child in later years.

Are there better fertility rates using electroejaculation or vibration? Does order of method influence outcome?

We were unable to locate any documents demonstrating a superior fertility outcome between vibration and electroejaculation. Therefore, we compared the side-effect profile of the two procedures to determine risk-benefit. Of the 21 studies identified that reported ejaculation rates with technique, 10 reported adverse events.[34-43] Often, authors combined procedures, although they did not always separate the side effects by procedure. However, papers that combined the procedures demonstrated that the vibration technique is less likely to be successful for lower motor neuron (areflexic) injuries than with spastic injuries, and electroejaculation is more likely than vibration to cause autonomic dysreflexia in patients with spastic injuries.[35,37] Electroejaculation also has the added side effects of inflammation to the rectal mucosa[39] and stimulation pain[34,38,39,44] in incompletely injured patients. Therefore, most clinics that combine these techniques usually try vibration first followed by electroejaculation in the areflexic subjects that tend to not respond to vibration alone.

To improve fertility rates, when should invasive techniques such as testicular biopsy or intracytoplasmic sperm injection be used?

Invasive techniques to enhance fertility (advanced fertility [AF] techniques) such as in vitro fertilization and ICSI have been used more in recent studies. By grouping the 18 studies above that reported either pregnancies or live births according to whether they used or did not use AF techniques, one can assess how using AF techniques impacts fertility rates. In doing so, one easily observes that to achieve pregnancy and birth rates approaching 50 percent or greater SCI couples need to use an AF technique. Testicular biopsy or vas aspirations should be reserved for those patients who cannot achieve sperm harvesting or whose harvested sperm by the above techniques is of very low quality. ICSI can greatly enhance success in those individuals whose sperm quality is insufficient for intrauterine insemination.

Are there pregnancy complications and prospective obstetric management issues for SCI females?

We did not find any reports that provided the necessary data for us to project the number and frequency of complications and other obstetric issues in females with SCI. There are numerous case reports, however, without the larger sample size obtained with a case-series study, it is difficult to conduct further research or inform practice or policy regarding this important health issue.

Question 2. How has the availability of Viagra® and other remediation affected sexual dysfunction and adjustment after SCI?

Interventions for female sexual dysfunction

We found six articles that used a case-control design[5,45-49] and one article that used a RCT design[50] to examine the phenomena of sexual arousal in response to physical and cognitive stimulation in women with SCI.

Male sexual dysfunction

Most of the literature discusses male erectile dysfunction after SCI. Aside from a number of RCTs evaluating Viagra®, all of the studies that we identified which addressed this topic were case-series studies. The most common problems faced when trying to analyze this literature is that many authors chose different outcome measures. For example, some authors use a validated erectile grading system such as Schramek's, whereas others used their own grading system; some authors used all or parts of the International Index of Erectile Function (IIEF) sexual satisfaction rating scale, whereas others designed their own scales. When authors use either an on/off grading system or a common question on the IIEF, we have pooled the data when appropriate. Interventions discussed in this review include: behavioral interventions, topical medications, intraurethral alprostadil, intracavernous injections, vacuum tumescence devices, penile implants, sacral stimulators, and Viagra® (sildafenil).

Is Viagra® really more benign than intracavernous injections?

Intracavernous injections have a significantly higher efficacy than Viagra® (90 percent versus 79 percent). To compare the side-effect profile of intracavernous injections with that of Viagra®, we extracted data from the studies described above that reported side effects. It can be noted that careful dosage adjustment is necessary with the papaverine or papaverine/phentolamine combinations. When used alone, prostaglandin E1 has few side effects outside of its cost. If subjects are reliable and if they have little sensation there seems to be few advantages of Viagra® over intracavernous injections aside from subject and partner preference. Although other phosphodiesterase inhibitors have come to market since sildanefil, no SCI treatment data for these drugs were available at the time of this review.

How does the morbidity of prostaglandin injections compare with the older, less expensive papaverine or phentolamine?

Although similar in efficacy, prostaglandin E1 is less stable at room temperature and much more expensive than papaverine or phentolamine. Proponents cite a shorter half-life (less chance of priapism) and less injection-site pain and scarring as reasons to use this substance despite its expense. We identified six noncomparative case-series studies[51-56] and one RCT[57] that reported the numbers of side effects. Although the efficacy of these two treatments is similar, priapism and discomfort are reported more frequently with papaverine.

What is the morbidity of vacuum tumescence devices?

When used with proper clinic instruction and according to the specifications of the manufacturers, these devices have a very low morbidity rate with no irreversible morbidities noted. Although there are case reports of penile ischemia in the literature, these case reports serve only as a warning not to leave the device on too long and cannot help us with ascertaining a complication rate.

What indications, if any, remain for implantable penile prosthetic devices?

It is notable that although penile implants result in a high level of satisfaction for those clients who do not have complications, the serious complication rate is as high as 10 percent. Furthermore, patients who have an implant removed are no longer candidates for other treatment options as they are likely to have damage to the penile tissues that would make them nonresponsive to intracavernous injections or vacuum devices. Very few patients will not respond to any of the more benign techniques.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center, Ottawa, Canada under Contract No. 290-02-0021. It is expected to be available in December 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 109, *Sexuality and Reproductive Health Following Spinal Cord Injury*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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