

# Stress urinary incontinence in women: Current and emerging therapeutic options

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Cite as: *Can Urol Assoc J* 2017;11 (6Suppl2):S155-8. <http://dx.doi.org/10.5489/cuaj.4613>

## Abstract

Surgical management of stress urinary incontinence (SUI) is most commonly achieved by midurethral synthetic sling (MUS) insertion as a first-line surgical option. A great deal of research continues to evolve new management strategies to reach an optimal balance of high efficacy and minimal adverse events. This expert opinion review provides a brief and comprehensive discussion of recent advances and ongoing research in the management of SUI, with an emphasis on single-incision mini-slings, vaginal laser treatment, and cell-based therapy. It is based on data obtained from numerous published meta-analyses and original studies identified through literature search. Single-incision mini-slings appear equally effective initially compared with standard MUS (retropubic or transobturator) for the treatment of female SUI; however, this efficacy lacks durability evidence beyond one-year followup. There is a lack of sufficient clinical evidence to currently confirm long-term safety and effectiveness of cell-therapy and non-ablative vaginal laser therapy, besides suggestion of apparent initial safety. There are still significant challenges to overcome before widespread clinical practice of the latter two modalities. Future research should be aimed at identifying groups of patients who might benefit from these minimally invasive therapeutic options.

## Introduction

Stress urinary incontinence (SUI) is a common condition that affects up about 250 000 Canadian women aged 65 and over.<sup>1</sup> Over the last three decades, several surgical procedures have been described in the literature for the treatment of SUI. Nowadays, midurethral slings (MUS) remain the surgical therapy of choice for SUI in women. New and minimally invasive methods have recently been introduced to optimize efficacy and overcome the complications and morbidity of standard therapies of SUI. The primary aim of our work was to provide a concise and directive summary of the evidence, together with suggested recommendations of new management strategies for SUI.

## Single-incision mini-slings

In an attempt to further decrease the morbidity associated with placement of traditional MUS, the current gold standard continence surgery for treatment of SUI related to urethral hypermobility,<sup>2</sup> the single-incision mini-slings (SIMS) have been developed as a conceivably safer and less-invasive surgical alternative for SUI. The insertion of shorter synthetic slings via a single vaginal incision avoids the retropubic space and obturator foramen, or groin muscles, in order to minimize postoperative pain and decrease operative time. It also has the potential to be performed as an outpatient procedure without sedation, which may offer short recovery and quicker return to normal activities. Theoretically, these potential benefits may improve health-related quality of life (HRQoL) and reduce the substantial economic burden on patients and the healthcare system.

A review of SIMS literature showed that most earlier randomized, control trials (RCTs) and meta-analyses were accompanied by inferior subjective and objective cure rates when compared with conventional MUS;<sup>3</sup> however, updated evidence demonstrates that, after excluding TVT-Secur<sup>®</sup> (withdrawn from clinical practice by the manufacturer), SIMS appear promising and lead to results comparable to the MUS in terms of patient-reported cure rates (risk ratio [RR] 0.94; 95% confidence interval [CI] 0.88–1.00) and objective cure rates (RR 0.98; 95% CI 0.94–1.01). This systematic review also showed a comparable impact on women's HRQoL, and sexual function at midterm followup (3–5 years) as MUS. Interestingly, it found a higher insignificant trend toward repeat continence surgery in SIMS group.<sup>4</sup> In different reviews, SIMS were associated with a more favourable postoperative recovery and lower incidence of perioperative complications.<sup>5</sup> The commercially available SIMS use the same tape material (type 1 polypropylene) and a similar surgical technique. Their anchorage mechanism, however, varies in their type/robustness.<sup>4</sup> Many recently introduced SIMS, such as Ajust<sup>®</sup>, Altis<sup>®</sup>, and TFS, allow a more precise tension adjustment and are designed to resist an intense pullout force;<sup>6</sup> however, meta-analyses of relevant RCTs

comparing adjustable SIMS to standard MUS showed no evidence of significant differences in short-term clinical outcomes (12 months).<sup>5,7</sup>

Newer versions of SIMS were designed without polypropylene anchors. For instance, Contasure-Needleless<sup>®</sup> were designed with “fascial pockets” on both ends and Ophira<sup>®</sup> was created with multiple projecting fixation points (except at the suburethral portion) to provide more post-insertion stabilization; however, in two different RCTs, Contasure-Needleless and Ophira failed to demonstrate any superior or even equivalent clinical outcomes compared to conventional MUS.<sup>8,9</sup> Also, it should be noted that the manufacturer withdrew the TVT-Secur from current clinical practice in response to poor clinical results at the midterm followup in 2013, after seven years on the market.<sup>10</sup> Boyers et al performed a health economic analysis of adjustable SIMS (Ajust) vs. MUS (TVT-O) to assess health-related costs in clinical practice. The results showed that SIMS-Ajust under local anesthesia was a cost-effective clinical strategy over a one-year followup period. More confirmatory economical models to estimate the long-term cost utility and outcomes of SIMS are required.<sup>11</sup>

In summary, SIMS were proven to have similar or at least non-inferior clinical efficacy compared with MUS within the first year; however, the limited long-term data weighs against its consideration as a surgical option, as we cannot predict the durability of its efficacy or its long-term safety. Some evidence suggests that SIMS were associated with a shorter operating time, significantly lower postoperative pain scores, and more favourable recovery time. Based on available data, there is no evidence of significant superiority of specific SIMS type in terms of clinical effectiveness or a more favourable adverse event profile. So far, generalizability of the results for patients and clinicians based on available evidence cannot yet be made.

### Non-ablative laser treatment

Recently, a novel, minimally invasive, non-surgical, non-ablative laser therapy was suggested as a treatment strategy for SUI. Laser technology employs a depth-controlled photothermal effect of the erbium-yttrium-aluminum-garnet (Er:YAG) laser with a  $\lambda=2940$  nm on vaginal mucosa and connective tissue, presumably by changing the architecture and composition of its extracellular matrix and improving its morphology and function. The thermal action of the laser primarily causes shrinkage of mucosa and underlying supportive tissue without destruction. It is also thought to cause mechanical pull of deeper tissue layers following the shrinkage, and activation of neo-collagenogenesis pathway, which further promotes the elasticity, thickness, and strength of the vaginal wall.<sup>12,13</sup>

Given that laser treatment of SUI is an innovative strategy, a few published exploratory pilot studies with small numbers

of patients and very short followup have demonstrated some improvement in SUI. The best level of evidence is from a recent prospective study by Ogrinc et al, in which 175 patients, newly diagnosed with SUI (66%) and mixed urinary incontinence (MUI [34%]) underwent an average of 2.5 (Er:YAG) distinct laser procedures over 12 months. Patients were evaluated with clinical examination, the International Consultation on Incontinence modular questionnaire (ICIQ), and Incontinence Severity Index (ISI). The authors reported that SUI significantly improved in 77% of the patients in all age groups, whereas only 34% of MUI patients showed no UI at one-year followup. Reported adverse events during laser procedure were minimal discomfort and/or pain.<sup>14</sup>

Similarly, all other initial clinical results of the SMOOTH mode Er:YAG laser vaginal treatment with IncontiLase<sup>™</sup> parameters demonstrated improvement of symptoms in a large majority of SUI-treated cohort. There were no adverse effects of this treatment reported in any of the studies, with an average of 6–12-month-lasting optimistic effects.<sup>15–17</sup> Likewise, Menachem et al did a retrospective study to evaluate pixel CO<sub>2</sub> laser (Alma) for strengthening and tightening the vaginal mucosa as a treatment of SUI. They reported a satisfactory global improvement of 66.7% at 12-month followup.<sup>18</sup> In a more comprehensive study, Tien et al objectively evaluated the effect of IncontiLase<sup>™</sup> laser technology for urodynamic stress incontinence. They concluded that IncontiLase procedure had moderate improvement for mild SUI only at six-month followup, but was futile for severe cases of SUI. It also meaningfully improved HRQoL and sexual function.<sup>19</sup>

To summarize, Er:YAG laser therapy is a minimally invasive, alternative treatment option for female SUI. Laser therapy yielded reasonable initial outcomes, alongside an acceptable safety profile and lower economic burden; however, we do not yet know which group of patients will respond better to this therapy, as the mechanism of action is still somewhat vague. Further RCTs are required to objectively assess the long-term sustained efficacy of laser treatment on SUI and the safety of repeated laser treatments, and also to compare its effectiveness on different SUI severity grades.

### Regenerative medicine and cell therapy

Currently, the application of regenerative medicine with targeted cell therapy for SUI attempts to halt disease progression and restore natural continence mechanism.<sup>20,21</sup> Classically, multipotent mesenchymal stem cells (MSCs) isolated from bone marrow stroma and skeletal muscle-derived cells (including myoblasts, muscle-derived stem cells [MDSCs], and fibroblasts) were the most investigated for their therapeutic application in SUI. Researchers continue to identify novel sources of stem cells for urological application, such as adipose-derived regenerative cells, umbilical cord blood stem cells, urine-derived stem cells, and total nucleated cells (TNCs) and platelets.

Although targeted cell therapy for SUI has been increasingly practiced in clinical trials, it is limited to a few non-randomized studies with small sample size, which demonstrate short-term safety and moderate efficacy results, comparable or even worse to those published on conventional urethral bulking.<sup>22,23</sup> Given the high success rate of MUS, which support the fundamental role of the pubourethral ligament (PUL) in continence control,<sup>24</sup> investigators have also focused on reconstruction with stem cells using a scaffold to construct a functional ligament de novo. Alternatively, some clinical trials targeted cell implantation into the urethral sphincter to restore the function of a weakened rhabdosphincter complex. Precise identification of SUI etiology (urethral hypermobility and/ or intrinsic sphincter deficiency [ISD]) is therefore necessary to target the scope of treatment toward the construction of neo tissue-engineered PUL or sphincter regeneration, or using both methods for mixed-etiology SUI.

Given the limited resources in literature, we appraised evidence from recent existing systematic review and some extensive narrative reviews. A recently published review article by Pokrywczynska et al,<sup>25</sup> analyzed clinical outcomes of 320 women with SUI treated using cell-based therapy. They reported a mean cure rate of  $41 \pm 30.7\%$  over a 12-month followup. As some of the included studies implanted stem cells combined with a bulking agent (collagen, adipose tissue), the reported success rate for the cell-only groups were even worse, at  $21.7 \pm 8.9\%$ . No major treatment-related adverse event was reported. Peters et al evaluated the safety and efficiency of autologous muscle-derived cells (MDCs) in urinary sphincter regeneration in 80 women with SUI over a 12-month period. They found that higher-dose groups ( $100 \times 10^6$  and  $200 \times 10^6$  MDCs) were associated with greater response in terms of reduction in SUI frequency and pad weight.<sup>26</sup>

Similarly, other clinical trials using myoblasts or MDSCs in treatment of female SUI were published by Blaganje et al,<sup>27</sup> Carr et al,<sup>28</sup> and Stangel-Wojcikiewicz.<sup>29</sup> All of them confirmed a high safety profile and encouraging short-term success rates in stem-cell-based therapy for SUI treatment. Unfortunately, cell isolation and culture strategies were not standardized and the number of implanted stem cells varied greatly between studies, making direct comparisons difficult to interpret. Nonetheless, the rates of stem cell viability and engraftment over a long-term period remain uncertain at this stage.<sup>30</sup> RCTs have looked at autologous muscle- and adipose tissue-derived cells, with one reported pooled data from two phase 1/2 studies following 80 women with SUI refractory to prior treatment. The data showed that injection of autologous muscle-derived cells did not lead to any adverse outcomes after 12 months of followup.<sup>26</sup>

In the near future, tissue engineering strategies may increasingly be applied, as various bioengineered degradable scaffolds have been proposed and studied in animal models.

The porcine small intestinal submucosa (SIS) is among the most commonly designed acellular scaffold; however, its application in SUI treatment is limited by extreme inflammatory events following its implantation without achieving desired results. Additionally, the SIS extracellular matrix mesh degrades rapidly by one month after grafting.<sup>31,32</sup>

In summary, application of cell-based therapy has demonstrated safety in the short-term, but does not support either strong or durable efficacy conclusions for SUI treatment. The ideal dosage of cells implanted, number of injection and the method of delivery are other important aspects that need to be standardized in future studies. We need to learn from our translational research to determine the best way to handle, produce and manufacture stem cells in order to optimize functionality in vivo in a clinical setting.<sup>33</sup> Finally, we need to clarify ethical and legal issues in the clinical application of regenerative medicine in SUI treatment, since an established gold standard modality (MUS) is available.

## Conclusion

There is a wide spectrum of surgical interventions available for women with SUI. Emerging surgical options, future targeted organ-specific therapy, and office procedures may offer promising options in order to improve patient satisfaction and safety. It is likely that office-based therapeutic options would become even more cost-effective for the management of SUI, as they are optimized in the future. The significant heterogeneity of the studies in the available literature highlights the need for caution in result interpretation. We therefore need more accurate targeted methodologies combined with high-quality trials with long-term results to determine if new strategies are equivalent or superior to the index procedure for the management of female SUI.

**Competing interests:** Dr. Campeau has been an advisor and speaker for Astellas and Pfizer; has received payment/grants/honoraria from Allergan, Astellas, Boston Scientific, and Pfizer; and has participated in clinical trials supported by Pfizer. Dr. Shamout reports no competing personal or financial interests.

This paper has been peer reviewed.

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