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Title

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Permalink

<https://escholarship.org/uc/item/33k4m4sp>

Journal

Obstetrical & Gynecological Survey, 75(1)

ISSN

0029-7828

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Publication Date

2020

DOI

10.1097/ogx.0000000000000761

Peer reviewed

if the trend continues. It is not clear that such findings would necessarily drive a return of the Uphold LITE or a similar device for use. In the meantime, surgeons will best serve their patients by continuing to open wide-ranging and

comprehensive discussions about goals and preferences with their patients wishing to consider surgery. No single option is ideal for every woman or without risk of recurrence or complications.—ACW)

Effect of Behavioral and Pelvic Floor Muscle Therapy Combined With Surgery Versus Surgery Alone on Incontinence Symptoms Among Women With Mixed Urinary Incontinence: The ESTEEM Randomized Clinical Trial

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JAMA 2019;322:1066–1076

ABSTRACT

It is estimated that urinary incontinence (UI) affects up to 58% of women and has a significant negative impact on their quality of life. Mixed UI includes both stress and urgency incontinence and is present in up to half of women with UI. Mixed incontinence is often considered more severe than UI, responds poorly to treatment, and is more difficult to manage than either urinary condition alone. Studies evaluating treatments that simultaneously improve both components of mixed UI are lacking. First-line treatment includes conservative therapy, behavioral and pelvic floor muscle training, followed by overactive bladder medication. Surgery with sling procedures can worsen urgency, and for this reason, clinical guidelines recommend treating the urgency component prior to consideration of surgery. Observational data support the effectiveness of midurethral sling surgery for treating the stress component. However, there are only limited data among women with mixed incontinence or approaches to improve urgency incontinence outcomes after midurethral sling. One strategy that has the potential to treat stress and urgency incontinence concurrently in women with mixed UI is combining conservative therapy with surgery, but the efficacy among women with mixed incontinence is unclear.

The aim of this multicenter, randomized, superiority trial was to determine whether combining behavioral and pelvic floor muscle therapy with midurethral sling is more effective than sling alone for improving UI symptoms in women with mixed

UI. Subjects were women 21 years or older, who reported moderately to severely bothersome symptoms of stress and urgency incontinence for at least 3 months and documented at least 1 stress and 1 urgency incontinence episode on a 3-day bladder diary. The study was conducted in the United States across 9 sites in the Pelvic Floor Disorders Network. Patients were enrolled between October 2013 and April 2016, with final follow-up in October 2017. Conservative therapy, behavioral and pelvic floor muscle therapy, included 1 preoperative and 5 postoperative sessions through 6 months combined with midurethral sling (n = 209) or sling alone (n = 207). Surgeons and outcome assessors were masked, but patients and interventionists were not. Change in mixed UI symptoms at 12 months, the primary outcome, was measured using the Urogenital Distress Inventory (UDI) long-form total score (range, 0–300 points; minimal clinically important difference, 35 points; higher scores indicate greater symptom severity).

Mean age was 54.0 (SD, 10.7) years. Of the 480 women randomized, 416 were eligible (209 combined, 207 sling only), had postbaseline outcome data, and were included in primary analyses. In the combined group, the UDI score significantly decreased (from 178.0 points at baseline to 30.7 points at 12 months); the adjusted mean change was –128.1 points, with a 95% confidence interval (CI) of –146.5 to –109.8.

In the sling-only group, the UDI score significantly decreased (from 176.8 to 34.5 points); the adjusted mean change was –114.7 points, with a 95% CI of –133.3 to –96.2. The model-estimated between-group difference of –13.4 points (95% CI, –25.9 to –1.0; $P = 0.04$) did not meet the minimal clinically important difference threshold for clinical importance. Serious adverse events occurred in 10.2% of the participants (8.7% combined and 11.8% sling only). Only 2.3% of these were considered to be possibly, probably, or definitely related to the intervention.

These data show that among women with mixed UI, behavioral and pelvic floor muscle therapy combined with midurethral sling surgery, when compared with surgery alone, resulted in a small statistically significant difference in UI symptoms at 12 months. The difference, however, did not meet the prespecified threshold for clinical importance.

EDITORIAL COMMENT

(Despite the significant prevalence and symptom bother of mixed UI in the overall population of women complaining of UI, consistent, evidence-based recommendations for treatment have been hard to establish. Traditional treatment algorithms have focused on segregating the overall symptoms into 2 categories (stress and urge), often with distinct plans for management. Often, pelvic floor physical therapy as the most noninvasive therapy is recommended first, to maximize treatment safety, but while it can be effective for both stress and urge UI (*Cochrane Database Syst Rev* 2010; CD005654), many women become dissatisfied with this initial form of treatment and move on. Regrettably, overactive bladder medications can be similarly ineffective or poorly tolerated in the long term (*Int J Clin Pract* 2011;65:567–585). Ultimately, many women with mixed UI resort to surgical treatment despite traditional teaching that it may worsen urge urinary incontinence (UUI) symptoms. Increasing evidence in the past 10 years has indicated this is not likely the case (*Int Urogynecol J* 2011;22:923–932), prompting more comfort with studying surgery as a treatment option for mixed UI.

Clinical trials for mixed UI have been hampered by hesitance to recruit women with significant severity of UUI, challenges in setting appropriate treatment outcomes, lack of power to detect both

SUI and UUI outcomes, and even lack of agreement on a definition of mixed UI. As an example, in 2009, the Urinary Incontinence Treatment Network published their experience with the MIMOSA trial protocol, which observed 27 women enrolled into a feasibility study over 4 to 5 months where the target study population for the main protocol was to be 1190. Problems were attributed to strict inclusion criteria, trial design, and divergent treatment approaches (*Clin Trials* 2009;6:355–364).

This study protocol was carefully designed and informed by these past experiences. The primary outcome at 1 year was chosen as the change from baseline in the Urinary Distress Inventory total score, because that scale is validated and patient reported and has subscales that reflect stress, irritative, and obstructive symptoms. The Urinary Distress Inventory discriminates between UI clinical groups and is responsive to clinical change. Inclusion and exclusion criteria were chosen to include women with significant severity of both stress and urge UI who were good candidates for surgical management of their SUI. Great care was taken to design a comprehensive program of combined behavioral and pelvic floor physical therapy, which could be standardized via a central training program but ultimately generalizable among pelvic floor therapists.

Ultimately, the ESTEEM study found that women with mixed UI who had perioperative behavioral and physical therapy around the time of their sling surgery did marginally better in controlling their UI symptoms than women who underwent sling alone, but the differences did not reach the level of clinical significance as defined by the study. Women in the combined therapy group did have slightly fewer UI episodes per day and were less likely to receive additional treatment for UI symptoms 1 year after surgery. The ESTEEM study did not show that urgency symptoms were worsened by sling surgery; in fact, the opposite was true. The improvement in mixed UI in women having sling alone was really quite consistent and is a striking finding. More than 80% of patients in both groups reported being globally much better or

very much better. The bottom-line treatment impact is that women with mixed UI should be evaluated to see if they are candidates for surgical management of their UI and can reliably expect improvement even when they have significant preoperative UUI. Taking the traditional stepwise approach by segregating the nature of UI symptoms can lead to unnecessary delay of surgery and therefore delay of relief. Some women with mixed UI will benefit from behavioral and pelvic floor physical therapy, which certainly can be offered as solo therapy in those who desire or used concurrently with surgery. This study did not evaluate whether women with persistent or worsening UUI symptoms post-sling surgery might benefit from postoperative behavioral and physical therapy, but clearly that option is safe to pursue.—ACW)

Vaginal Bromocriptine Improves Pain, Menstrual Bleeding, and Quality of Life in Women With Adenomyosis: A Pilot Study

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Acta Obstet Gynecol Scand 2019;98:1341–1350

ABSTRACT

Animal models suggest that increased uterine prolactin concentration is a risk factor for adenomyosis. Prolactin is produced in the human endometrium, myometrium, and the pituitary gland and acts as a smooth muscle cell mitogen in vitro. Both murine and human studies suggest a link between the action of antidepressants and prolactin in the development of adenomyosis. Bromocriptine, a dopamine agonist, inhibits pituitary secretion of prolactin and is the criterion standard of treatment for hyperprolactinemia. This agent is inexpensive and safe and has no serious adverse effects.

The aim of this pilot study was to evaluate the effect of bromocriptine on menstrual bleeding and pain in women with adenomyosis. Participants were 23 women aged 35 to 50 years with diffuse adenomyosis characterized by regular heavy menstrual bleeding (HMB). Patients were enrolled from a university hospital in Sweden and a tertiary care hospital in the United States. A total of 19 patients completed 6 months of treatment with vaginal bromocriptine 5 mg daily. Study staff and participants were not blinded to treatment. Several self-administered validated questionnaires were utilized to assess changes in symptoms from baseline to 3 and 6 months of treatment and at 9 months (3 months after cessation of bromocriptine). The questionnaires included Pictorial Blood Loss Assessment Chart (PBLAC), Aberdeen Menorrhagia Clinical Outcomes Questionnaire, visual analog scale for pain, McGill Pain Questionnaire, Endometriosis Health Profile (EHP-30), Female Sexual Function Index, and the Fibroid Symptom Quality of Life (UFS-QOL) symptom severity and health-related quality-of-life subscores. The Wilcoxon signed rank test was used to compare scores between baseline and 9 months. All treatment scores were compared with baseline.