Original article

Transurethral bulking agent injection in female stress urinary incontinence: long term results using Opsys®

MIGUEL ANGEL ZANGONE[1], TOMÁS OLMEDO[2], MAURICIO OLEA[2]

[1]*Hospital Bernardino Rivadavia, Buenos Aires, Argentina*
[2]*Hospital San José - Urology Unit and Urology Department of Hospital Clínico of the University of Chile, Santiago, Chile*

Abstract. *Objective*: assessment the long term clinical effectiveness of the Opsys® bulking agent used as injectable therapy in the treatment of female stress urinary incontinence (SUI). *Patients and Method*: a total of 38 women with SUI were prospectively included in this non-randomized, open, multicenter study after having signed an informed consent form. The subjects' mean age was 62.6 years, and the mean body mass index (BMI) was 31.8 kg/m^2. One woman was lost to follow-up 12 months postoperatively. The preoperative evaluation included a physical examination, a 24-hour pad weight test (PWT), a Q-Tip test, Valsalva leak point pressure (VLPP) with urodynamic studies and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF[1]). Patients were followed-up for a total of 60 months, and these results were compared to those obtained at 12 months. Thirty-three patients (86.8%) underwent a single implant procedure, the remaining five cases (13.2%) received a second implantation. *Results*: Sixty months after surgery, the 24-hour PWT showed 46% of patients being dry, 27% improved, and 27% failed producing a 73% cure rate (dry+improved). The ICIQ-SF at 60 months showed a mean value of 10.1 (SD=6.2) compared to the preoperative mean value of 18.0 (SD=2.4). Nine patients (23.7%) presented with *de novo* urge incontinence, and 7 (18.4%) had transient urinary retention. Urinary tract infections (UTI) were confirmed in 3 cases (7.4%) and dysuria in 4 (10.5%). *Conclusions*: Opsys can be offered as a minimally invasive procedure with durable clinical results.

Key words: SUI; Heterologous material; Bulking agent; Biocompatible: Polyacrylate polyalcohol.

Acronyms: BMI: Body Mass Index; ICIQ-SF: International Consultation on Incontinence Questionnaire – Short Form; ISD: Intrinsic Sphincter Deficiency; PWT: Pad Weight Test; SUI: Stress Urinary Index; VLPP: Valsalva Leak Point Pressure.

INTRODUCTION

The main objective of this work has been to assess long term clinical effectiveness of the Opsys bulking agent as an injectable therapy used in the treatment of SUI. It is important to initially comment that ISD is a relevant component in SUI, and, thus, its assessment is highly valuable. SUI due to ISD is defined as the presence of a urethral sphincter mechanism that fails to maintain sufficient resistance for urinary continence either at rest or in the presence of minimal physical exertion.[1] Surgical treatment of SUI is generally prescribed after conservative treatments, such as biofeedback and drugs, have failed. These surgical procedures can be divided into three groups: suburethral slings, colposuspension procedures and periurethral injections. The sling is currently considered as the "gold standard" for SUI treatment.[2]

For the past twenty years, the trend has been to develop less invasive procedures with similar cure rates when compared to sling placement or Burch techniques but with the advantage of reducing morbidity, hospitalization and convalescence before returning to normal activities.[3] Transurethral injections via urethroscopy have the significant advantage of being less invasive and easily performed when compared to slings or Burch techniques.[4] The injection of bulking agents through urethroscopy has been studied and utilized for more than 65 years[5] during which time a variety of different substances have been tried. In the last decades, different substances have been tested including autologous fat,[6] polytetrafluoroethylene paste,[7] bovine collagen, silicon elastomer,[8] dextranomer copolymers (DiHA), polyvinyl alcohol foam, calcium hydroxyapatite (CaHA), myoblasts (stem cells)[9] and chondrocytes.

Patient selection is a critical factor in determining objective and subjective success of transurethral bulking agents. The advantages of such a procedure are clear, but not all women are equally suitable for this treatment. This therapy is indicated for women who want or need a less-invasive procedure, who may be an anesthetic risk, who may have had a previous sling procedure failure, for those patients with multiple co-morbidities or for young women who may want to achieve future pregnancies.[10]

PATIENTS AND METHODS

Results were collected from an open, single-arm, non-randomized, multicentric study. A total of 38 female patients with SUI who had ISD as the main component of incontinence and had completed a 60 month follow-up were included in this study. One patient was lost to follow-up 12 months postoperatively. The mean age of the patients was 62.6 [42-92] years, and the mean BMI was 31.8 [22-49] kg/m^2. 80% of the patients enrolled in the study were postmenopausal, and 6/38 subjects had an initial diagnosis of mixed incontinence. Although incontinence was due predominantly to ISD, 4/38 were treated with antimuscarinics before undergoing the Opsys procedure. Other baseline information is summarized in Table 1.

The bulking agent substance used in this study is made of a polyacrylate polyalcohol copolymer, which is a non-absorbable biomaterial[11] also used in children to treat vesicourethral reflux conditions.[12,13] The macroparticles of Opsys have an average diameter of 300 μm, and they are hydrated in a 40% glycerol solution. This combination leads to a substance which can be manually injected easily through small needles (21-gauge). The biocompatibility and non-migration characteristics as well as long-term bulking stability in the implant site of the substance have been proven by both *in-vivo* and *in-vitro* studies.[11]

Preoperatively, patients were questioned using the ICIQ-SF and were objectively evaluated through the 24-hour PWT.[14] Urodynamics was verified by a complete physical examination which involved: cystometry with measurement of leakage pressure, profilometry with evaluation of urethrovesical differential pressure in active phase, maximum pressure of urethral closing in active/passive phase and functional length. Valsalva leak point pressure (VLPP) was measured in each patient after the bladder was filled with 200 mL

TABLE 1. – Baseline characteristics of patients and preoperative assessments.

Characteristic	N	Mean	SD	Min-Max	% (N/N_{TOTAL})
Women recruited	38	-	-	-	100.0
Age - years	-	62.6	10.1	42-92	-
Body Mass Index - kg/m^2	-	37.6	8.5	22-55	-
Parity	-	2.4	1.1	1-6	-
Menopausal	31	-	-	-	79.5
Type of Urinary Incontinence					
Mixed Incontinence	6	-	-	-	15.8
ISD Incontinence	32	-	-	-	84.2
VLPP - cmH_2O	-	46.8	11.0	27-65	-
Cases treated with antimuscarinics	4	-	-	-	10.5
Previous anti-incontinence surgery	4	-	-	-	10.5
Burch	1	-	-	-	2.6
Sling	3	-	-	-	7.9
ICIQ-SF	-	18.0	2.4	11-21	-
Maximum Flow - mL/s	-	25.5	2.9	20-30	-
Urine leakage - g/day	-	108.6	69.5	34-300	-

of saline solution. Patients were diagnosed with SUI due to ISD when VLPP was lower than or equal to 60 cmH_2O and primary urethral hypermobility was discarded (Q-tip>30°).

Opsys implantation was performed transurethrally under direct vision using a rigid cytoscope with 30º angle optics. General anaesthesia was the most commonly used technique (38.5%) followed by neuroleptoanaesthesia (30.8%), spinal (23.1%) and peridural (7.7%). Transurethral injection sites were identified at the 2-, 6-, and 10-o'clock positions (injecting ≥ 1 mL, ≥ 2 mL and ≥ 1 mL respectively) one centimeter from the bladder neck in the submucosal region of the proximal urethra. Figure 1a and Figure 1b show the cystoscopic image of the urethral lumen before and after the bulking agent was injected.

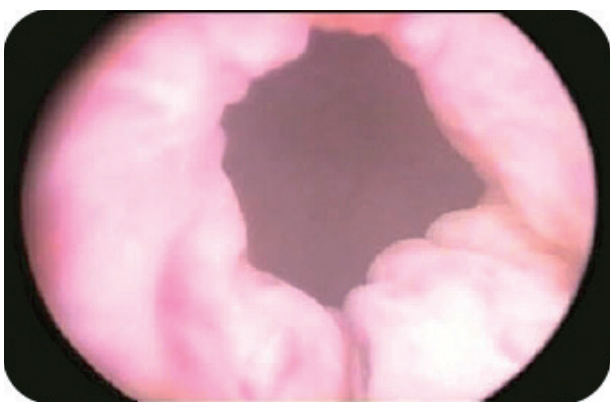

Figure 1. – *1a* Cystoscopic image before the bulking agent was implanted.

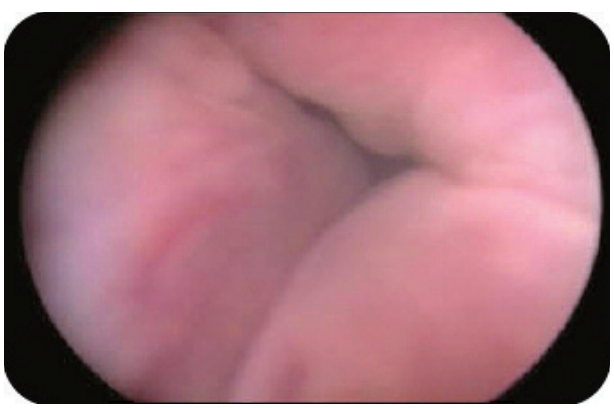

Figure 1. – *1b* Cystoscopic image after the bulking agent implantation.

Postoperative follow-up of patients was performed at a physician's office repeating both the questionnaire (ICIQ-SF) and 24-hour PWT at 3, 6, 12, and 60-months. Patients were considered objectively dry when the post-operative 24-hour PWT resulted in less than 1.3 g of urine loss.[14] If the loss represented a reduction of more than 50% from the initial preoperative measurement, the patients were classified as improved.[15] Patients were considered as having failed if they did not meet either of the previous criteria.

A re-implantation procedure was offered 90 days post-procedure to those patients who did not get a positive result and it was performed upon patient's consent.

A comparison between the 60-month and 12-month data was done using a paired-samples Student t-test in IBM SPSS Statistics 17 with a significance level of 0.05.

RESULTS

Thirty-three on 38 patients (86.8%) underwent a single implant procedure. The median volume of injected material was 4.8 mL. Sixty months postoperatively, 46.0% of the patients were completely dry, and 27.0% met the criteria to be considered improved. These numbers indicate a 73% cure rate (dry+improved) and a 27% failure rate based on the

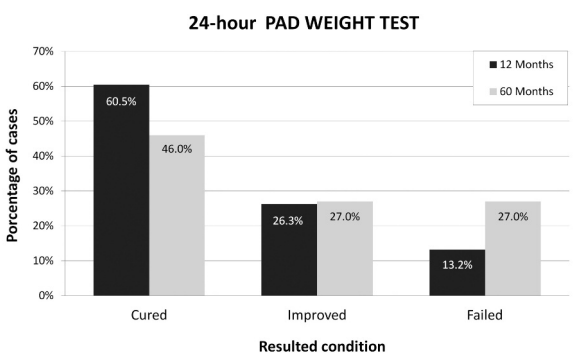

Figure 2. – Mean values of cured/improved/failed rates obtained from the 24-hour Pad Weight Test.

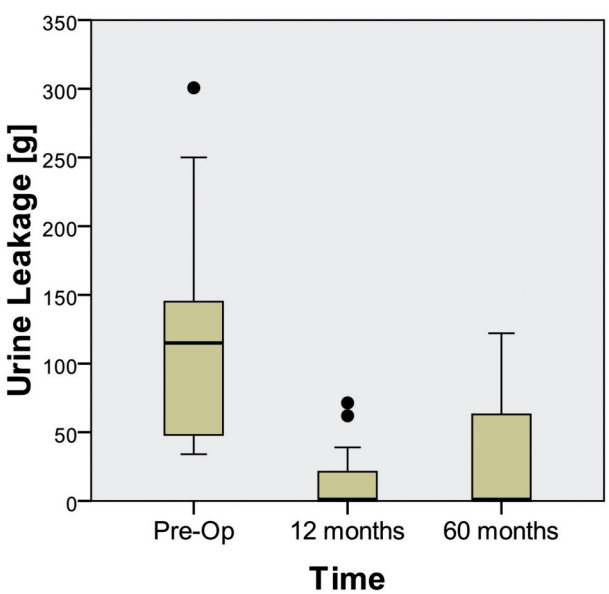

Figure 3. – Urine leakage measured with the 24-hour Pad Weight Test.

Table 2. – Complications.

Adverse event	N	%
Urinary tract infection	3	7.9
Urinary retention	7	18.4
De novo urge incontinence*	9	23.7
Dysuria	4	10.5

*At 12 months, only 2 (5.3%) of these women had presented with this condition. The other 7 (18.4%) reported their first symptoms 60 months postoperatively.

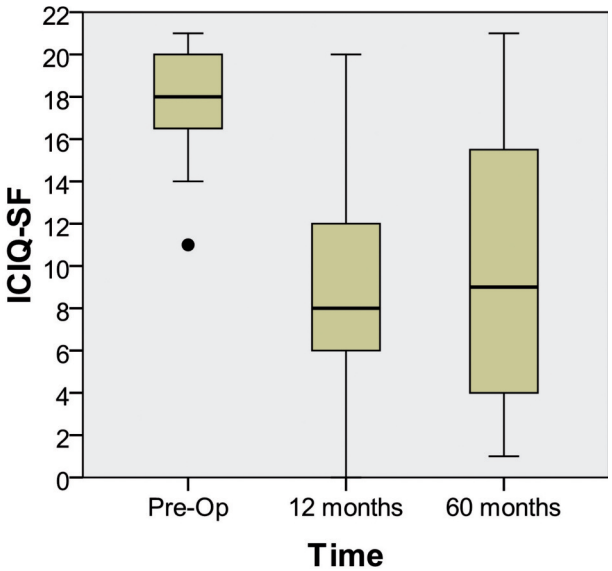

Figure 4. – Results obtained for the ICIQ-SF.

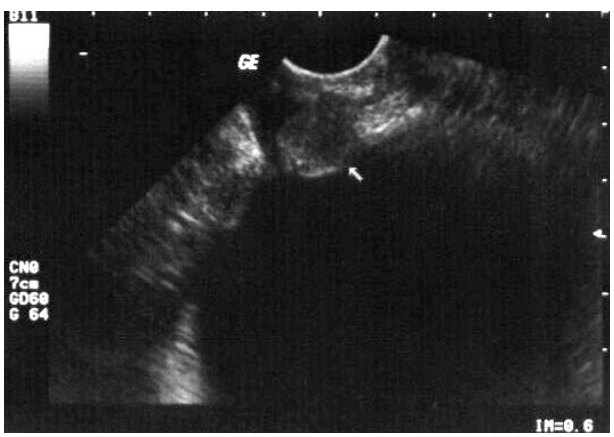

Figure 5. – Patient's transvaginal ultrasound performed 3 months after implant procedure. The image clearly shows the presence of the implanted substance (arrow), which confirmed the permanence of the resulting bulk.

objective measurement of a 24-hour PWT. Figure 2 shows these results in terms of percentage rates, and they are paired to the results obtained at 12 months. The paired-samples Student t-test did not show a statistically significant difference between these measurements (*p=0.209 two-tailed test*). Figure 3 shows the comparison of urine leakage in grams. Five patients (13.2%) underwent a re-implantation procedure 90 days after the surgery. Among these 5 patients, 2 became dry, 1 improved her condition, and the other 2 patients remained incontinent.

The ICIQ-SF at 60 months resulted in a mean value of 10.1 (SD=6.2) compared to the original mean value of 18.0 (SD=2.4). The mean value registered for the 12-month follow-up was 8.4 (SD=5.5). These follow-up differences were found not to be statistically significant (*p=0.593 two-tailed test*) indicating stability in patient perception of the implantation outcomes. Figure 4 shows the results of ICIQ-SF arranged in a box plot graph. The median value for 12 months and 60 months were 8 and 9 respectively (pre-operative median value was 18).

Complications are summarized in Table 2. Two patients (5.3%) presented with *de novo* urge incontinence at 12 months. The number of patients with *de novo* urge incontinence increased up to 9 (23.7%) after the 60-month follow-up. Seven patients (18.4%) had urinary retention in the first 48 hours, and intermittent sterile catheterization had to be performed during that time to resolve this complication. Three cases of urinary tract infections were reported; all were resolved with antibiotics. Dysuria was identified in 4 patients (10.5%).

DISCUSSION

The goal of SUI treatment is to increase urethral resistance to achieve continence during intra-abdominal pressure variation. This is obtained through coaptation or narrowing of the urethral lumen and by increasing urethral closure pressure.[16] The gold standard treatment in this type of pathology is sling implantation with success rates over 70%.[17,18] However, patient demands for less invasive procedures and decreased morbidity postoperatively have resulted in renewed interest in bulking agent treatments. A variety of both absorbable and non-absorbable bulking agents have been tested throughout the years. The published success rates range from as low as 7% to 83%. The latter success rate of 83% was observed in absorbable substances with a short term follow up, the values of which significantly decreased within 9 to 19 months after the substance was initially injected.[19]

In our study, an objective dry/improvement rate of 73% was measured 60 months after the implantation of Opsys. When compared to the 12-month results, no significant statistical difference was found. Other authors have published subjective success rates at 60 months with silicone elastomer macroparticles from 29%[20] to 80%.[21] The latter rate corresponds to a study with a re-injection rate of 38%. In this study with Opsys, a second procedure was performed in 5 (13.2%) patients compared to reported rates up to 49%[22] for silicon elastomer and reaching a 35% with a polyacrylamide substance.[23]

Radiographic imaging and ultrasonagraphy are common techniques used to verify the presence of a bulking site formed by different transurethral injectable substances. Opsys is not radiopaque, but it can be seen via ultrasound after the first 3 months post-injection. The image of Figure 5, taken 3 months after the implantation, shows the presence of the heterologous material in the perivesical, suburethral region. This photo was obtained by using transvaginal ultrasound performed with a 7 MHz transducer. The use of ultrasound imaging can be used before executing a second injection in order to verify the presence of the bulking agent at the initial sites and the appropriateness of their positions.

Sixty months postoperatively, an anticipated loss of efficacy in some subjects was noted for this bulking agent treatment. One factor which might be partially responsible for this loss of continence was the appearance of an important number of *de novo* urge incontinence cases. In fact, only 2 cases (5.3%) of *de novo* urge incontinence were registered at the 12-month follow-up, while 7 (18.4%) were registered at the 60-month follow-up for a total of 9 (23.7%) cases of patients with urge incontinence (Table 2). When using a silicone elastomer bulking agent, a 4.9% incidence of *de novo* urge incontinence was registered at 12 months,[8] and 50% incidence was found in a 60-month, follow-up study.[20] The dif-

ference in the number of new urge incontinence cases may be supported by epidemiological evidence which highlights the correlation of urge incontinence prevalence with age. Our study population presented a preoperative mean age of 62.6 years, and with the additional 60-month follow-up, the average age became 67.6 years. According to the NOBLE Study (National Overactive Bladder Evaluation), the prevalence of urge incontinence for 45-64 year old U.S. women was approximately 13%; this prevalence increases to 19% for women within an age range of 65-74 years.[24] Several other studies[25] support this correlation of urge incontinence with age although the rates may differ depending on the study design and the definition of overactive bladder symptoms. When evaluating the signs and symptoms of the study patients who presented with urge incontinence at their last follow-up, it was concluded that there was strong evidence that these symptoms could represent an additional, independent condition that had no relationship to the pathophysiology of the patient's original SUI condition or to the therapeutic application of the bulking agent. Women are more likely to suffer from other systemic pathologies as they age which negatively impact the inhibitory influence of the supraconal levels of the central nervous system over the spinal cord cone (medullary micturition center, S2/S3). This loss of inhibition would not be directly associated to the vesicourethral anatomic alteration due to an injectable substance even when these conditions produce the same symptomatology as the primary condition (SUI) as the involuntary loss of urine.

Based on this study's results, the authors believe that Opsys can be used as a minimally invasive transurethral bulking procedure with durable clinical results and no serious adverse events. Additionally, another important point to be considered when reviewing our results is the low re-injection rate registered in this study which makes Opsys a robust option as a single injection treatment.

ACKNOWLEDGEMENTS

GRANTS OR FINANCIAL SUPPORT: Promedon S.A. has funded the investigation. The authors have not reported any financial relationship with Promedon S.A. or other conflicts of interest.

REFERENCES

1. Agency for Health Care Policy and Research. Urinary incontinence in adults: clinical practice guideline. AHCPR Publication Nº 92-0038. Rockville, Maryland: Agency for Health Care Policy and Research, Public Health and Human Services, 1992.
2. Bemelmans B.L.H., Chapple C.R. Are slings now the gold standard treatment for the management of female urinary stress incontinence and if so which technique? Curr Opin Urol, 2003; 13: 303-7.
3. Balmforth E., Cardozo L.; Trends towards less invasive treatment of female stress urinary incontinence, Urology, 2003; 62 (Suppll 4A): 52-60.
4. Maman J.T.N., D'Ancona C.A.L., Tadini V., Netto N.R.; Macroplastique implantation system for the treatment of female stress urinary incontinence; J Urol; 2003; 169: 2229-2233.
5. Benshushan A., Brzezinski A., Shoshani O., Rojansky N.; Periurethral injection for the treatment of urinary incontinence; Obstet Gynecol Surv, 1998; 53: 383-8.
6. Nilsson C.G., Kuuva N., Falconer C., et al; Long-term results of tension free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence; Int Urogynecol J Pelvic Floor Dysfunct 2001; 12 (Suppl): 5-8.
7. Palma P.C.R., Riccetto C.L.Z.; Injeçoes periuretais no tratamento da incontinência urinária de esforço. In: Aplicações Clínicas da Urodiâmica; Ed 3. São Paulo: Atheneu, 2001; 167-74.
8. Ghoniem G., Corcos J., Comiter C., Bernhard P., Westney O., Herschorn S.; Cross-Linked Polydemethylsiloxane injection for female stress urinary incontinence: Results of a multicentric, randomized, controlled, single-blind study. J Urol 2009; 181: 204-10.
9. Radley S.C., Chapple C.R., Mitsogiannis I.C., Glass K.S.; Transurethral implantation of macroplastique for the treatment of female stress urinary incontinence secondary to urethral sphincter deficiency; Eur Urol 2001; 39: 383-9.
10. Ramsden M., Williams E., Siegel S.; Female Stress Urinary Incontinence: Office based Urethral Bulking Agent Procedure; Urol Nurs 2010; 30: 297-305.
11. Ormaechea M., et al, VANTRIS®, a biocompatible, synthetic, non-biodegradable, bulking substance, easy to inject. Evaluation of local reaction, localized migration and long-distance migration; Ach Esp Urol 2008; 61: 263-8.
12. Ormaechea M., Ruiz E., Denes E., Gimenes F., Dénes F., Moldes J., Amarante A., Pioner G., Dekemacher S., de Badiola F.; New tissue bulking agent (polyacrylate polyalcohol) for treating vesicourethral reflux: Preliminary results in children. J Urol 2010; 183: 714-17.
13. Chertin B., Arafeh W.A., Zeldin A., Kocherov S.; Preliminary data on endoscopic treatment of vesicoureteric reflux with polyacrylate polyalcohol copolymer (Vantris): Surgical outcome following single injection; J Pediatr Urol 2011; 7: 654-7.
14. Tubaro A., et al. Imaging and other investigations, Chapter in Incontinence 4th Ed. Abrams P., Cardozo L., Khoury S., Wein A. (Eds.). Health Publications Ltd, 2009. Committee 7B: 541-630.
15. Clinical investigations of devices indicated for the treatment of urinary incontinence - Guidance for industry and FDA staff. Document issued on March 8, 2011. US Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health.
16. Haab F., Zimmern P.E., Leach G.E.; Female stress urinary incontinence due to intrinsic sphincteric deficiency: recognition and management; J Urol 1996; 156: 3-17.
17. Bergman A., Elia G.; Three surgical procedures for genuine stress incontinence: five years follow-up of a prospective randomized study; Am J Obstet Gynecol 1995; 173: 66-71.
18. McGuire E.J., Bennett C.J., Konnak J.A., Sonda L.P., Savastano J.A.; Experience with pubovaginal slings for urinary incontinence at the University of Michigan; J Urol 1987; 138: 525-6.
19. Appell R.A.; Periuretral injection in urogynecologic surgery: The masters techniques in gynecologic surgery; 2nd ed. Edited by W. G. Hurt. Philadelphia: Lippincott Williams & Wilkins, 2000, p. 149.
20. Maher C.F., O'Reilly B.A., Dwyer P.L., Carey M.P., Cornish A., Schulter P.; Pubovaginal sling versus transurethral Macroplastique for stress urinary incontinence and intrinsic sphincter deficiency: a prospective randomised controlled trial; BJOG 2005; 112: 797-801.
21. Tamanini J.T.N., D'Ancona C.A.R.L., Netto N.R.; Macroplastique implantation sistem for female stress urinary incontinence: Long-Term Follow-Up; J Endourol 2006; 20: 1082-6.
22. Ghoniem G., Corcos J., Comiter C., Westney L., Herschorn S.; Durability of urethral bulking agent injection for female stress urinary incontinence: 2-year multicenter study results; J Urol 2010; 183: 1444-9.
23. Lose G., Sorensen H.C., Axelsen S.M., Falconer C., Lobodasch K., Safwat T.; An open multicenter study of polyacrylamide hydrogel (Bulkamid®) for female stress and mixed urinary incontinence; Int Urogynecol J 2010; 21: 1471-77.
24. Stewart W.F., Van Rooyen J.B., Cundiff G.W., Abrams P., Herzog A.R., Corey R., hunt T.L., Wein A.J.; Prevalence and burden of overactive bladder in the United States; World J Urol 2003; 20: 327-36.
25. Shamliyan T., Wyman J., Bliss D.Z., Kane R.L., Wilt T.J.; Prevention of fecal and urinary incontinence in adults; Evidence Report/Techonology Assessment N° 161 (Prepared by the Minnesota Evidence-based Practice Center). AHRQ (Agency for Healthcare Research and Quality), 2007. Publication N° 08-E003. Rockville, MD.

Correspondence to:
MIGUEL ANGEL ZANGONE
Av. Las Heras 2670.
Buenos Aires (C1425ASQ) Argentina
E-mail: miguelzangone@gmail.com