inFlow Clinical Publications

Clinical Studies

1. Schimke L, Connolly K. *First Report: U.S. Clinician and Patient Experiences with the inFlow™ Urinary Prosthesis for Permanent Urinary Retention in Women.* Urologic Nursing. Mar/Apr2020, Vol. 40 Issue 2, p61-84. 14p. https://library.suna.org/suna/search/0/query?tag=urinary%20prosthesis
2. FDA Center for Devices and Radiological Health, *DEN130044_Vesiflo_inFlow_de_novo_summary*. Oct 2014 https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130044.pdf
3. Chen TYH, Ponsot Y, Carmel M, Bouffard N, Kennelly MJ, Tu LM. *Multi-Centre Study of Intraurethral Valve-Pump Catheter in Women with a Hypotonic or Acontractile Bladder.* Eur Urol 2005; 48: 628-633. DOI: 10.1016/j.eururo.2005.04.020
4. Mazouni C; Karsenty G; Bladou F; Serment G. *Urethral device in women with chronic urinary retention: an alternative to self-catheterization?* Eur J Obstet Gynecol Reprod Biol 2004; 115(1): 80-84 DOI: 10.1016/j.ejogrb.2003.10.031
5. Lynch WJ, Testa GA, Bell D: *A Study to Determine Subjective and Objective Benefits of a Remote-Controlled Intra-Urethral Device for the Management of Female Acontractile Bladder.* Brit J Urol 2003; 92: 960-963. DOI: 10.1111/j.1464-410x.2003.04525.
6. Madjar S, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *Long-term follow-up of the inFlow™ intraurethral insert for the treatment of women with voiding dysfunction.* Eur Urol 2000; 38:161-166.
7. Madjar S, Sabo E, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *A remote controlled intraurethral insert for artificial voiding - A new concept for treating women with voiding dysfunction.* J Urol 1999; 161:895-898.
8. Schurch S, Suter S, Dubs M: *Intraurethral sphincter prosthesis to treat hyporeflexic bladders in women – Does it work?* Brit J Urol 1999; 84:789-794.
9. Nativ O, Moskovitz B, Issaq E, Condrea A, Kastin A, Halachmi S, Burbara J, Madjar S, Beyar M: *A new intraurethral sphincter prosthesis with a self-contained urinary pump.* ASAIO J 1997; 43:197-203.

Review Article

- Hartigan SM, Reynolds WS, Dmochowski RR. *Detrusor underactivity in women: A current understanding.* Neurourol Urodyn. 2019 Nov;38(8):2070-2076. https://doi.org/10.1002/nau.24147 PMID: 31432566.

Textbook Chapter

- Chancellor M.B. (2016) Advance Technology. In: Chancellor M., Diokno A. (eds) *The Underactive Bladder*. Springer, Cham. https://doi.org/10.1007/978-3-319-23687-2_10

Podium Presentations at Medical Conferences

1. inFlow™ Urinary Prosthesis: Restoring Function and Dignity to Women with Permanent Urinary Retention. Medicare DME Medical Directors Meeting, Urological Supplies (2020) https://med.noridianmedicare.com/web/jadme/policies/lcd/open-meeting/urological-open-meeting-012820
2. Simon Foundation Conference, April 21, 2017. *"The inFlow Urinary Prosthesis: Restoring Function and Personal Dignity to Women Who Need Urinary Catheters."* Connolly KM
3. American Urological Association, May 7, 2016. *"Innovative Solutions for Chronic Urinary Retention in Women: Intraurethral Valve-Pump."* Kennelly M.
4. 2nd International Congress on Underactive Bladder, Dec. 5, 2015. *"Reinventing Bladder Drainage: The inFlow Urinary Prosthesis for Women and Guardian VCS."* Connolly KM.

Case History: MS Patient

- "HealthLink," a news program of Seattle NBC affiliate KING-TV, May 26, 2016. *inFlow: An MS Patient's Story*. https://vesiflo.com/videos/

Summary of Clinical Studies

Chen TYH, Ponsot Y, Carmel M, Bouffard N, Kennelly MJ, Tu LM. *Multi-Centre Study of Intraurethral Valve-Pump Catheter in Women with a Hypotonic or Acontractile Bladder.* Eur Urol 2005; 48: 628-633.
DOI: 10.1016/j.eururo.2005.04.020

This is a preliminary report of the prospective, multi-center study establishing the value of this device-based procedure.

Study protocol: This study compared the safety and effectiveness of the inFlow to the current standard of care, clean intermittent catheterization (CIC), per a study protocol directed by the FDA. As it was not practical to create an indistinguishable comparator, this study used a crossover design with a single cohort, but that cohort was limited to women who were successfully using CIC as their normal method of bladder drainage (some for as long as 20 years). Baseline/CIC use was tracked for 8 weeks and subjects were then crossed over to Treatment/inFlow for 16 weeks.

Results: Almost 100% of subjects met the primary endpoint (post-void residual, PVR) and the inFlow improved quality of life by 60% compared to CIC. The FDA took particular note of one safety finding: *"The most potentially significant adverse event – UTI – appears lower with the inFlow device than with CIC, was stable with time, and was easily managed with antibiotics."* As prospectively estimated based on experience with this and other neuro-uro interventions, the rate of device discontinuance was high, but was comparable to that of CIC per numerous other studies. No serious or long-lasting adverse events associated with device use were reported and 97% of subjects who completed the study elected to continue using the device.

FDA Center for Devices and Radiological Health, *DEN130044_Vesiflo_inFlow_de_novo_summary.* Oct 2014 https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130044.pdf.

As part of its review, The FDA published a more comprehensive description of the inFlow's pivotal trial. The FDA had classified the inFlow Urinary Prosthesis as a Class III device and required this pivotal trial in support of a PMA application. Following a lengthy review that was eventually resolved at the highest level of the agency, the inFlow was down-classified to Class II and became one of the FDA's first De Novo approvals.

Table 1. Key Findings from FDA Review[13]

- Effectiveness
  - *"the inFlow device was able to empty the bladder of urine as well as CIC, with a higher quality of life"*
- Safety
  - *"While adverse events were not infrequent with use of the inFlow device, they were mild to moderate in severity and were easily resolved."*
  - *"The most potentially significant adverse event – UTI – appears lower with the inFlow device than with CIC, was stable with time, and was easily managed with antibiotics."*
  - *"Cystoscopic evaluation revealed no evidence that use of the inFlow device alters the urethra or bladder mucosa."*
  - *"Of note, no inFlow device failed due to encrustation."*
  - *The inFlow device can be easily removed at any time by the patient or caregiver."*
    - *"Following removal, any complications that occur… resolve or can be readily treated."*
- Summary
  - *"Although the discontinuation rate documented in the clinical trial increases the uncertainty in the observed results, the inFlow device provided a wide margin of effectiveness and a clinically acceptable risk profile."*

Note: *"The risks and benefits of the device are based on the non-clinical laboratory studies, as well as the data collected in the pivotal and supporting clinical studies. In all studies, the device effectively emptied the bladder."*

13. FDA Center for Devices and Radiological Health, *DEN130044_Vesiflo_inFlow_de_novo_summary*. Oct 2014 https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130044.pdf

Table 2. Supporting Clinical Studies

- Six non-comparative clinical studies (total *n*=228) with similar populations to the pivotal have been published in major peer-reviewed journals
  - Results were similar - no serious or lasting adverse events were reported, reported UTI rates were consistently low and best practice became better understood over time

PI/Lead Author	Journal	Study Size	UTI Rate*	Key Findings/ Conclusions
Lynch	British Journal of Urology	20	0.01	Lynch reported that 14 evaluable subjects had a total of 2 UTIs in 156 subject-months (0.01% incidence), almost no device-related dropout, 80% quality of life improvement per Wagner I-QOL scores, no negative tissue changes and concluded that *"the (inFlow) device provides an effective method of bladder drainage, with few side-effects and significant improvement in QoL."*
Mazouni	European Journal of Obstetrics and Gynecology	60	0.03	Mazouni reported that although 30 subjects dropped out <15 days, 30 evaluable subjects had a total of 6 UTIs in 178 subject-months (3.4% incidence) and concluded that inFlow is *"An attractive, simple technique for use as an alternative to catheterization."*
Madjar	European Urology	21	0.01	Madjar reported that when 21 subjects from his two-part study continued on-device, they had a total of 4 UTIs in 517 subject-months (0.01% incidence) and concluded that, although dropout was a problem (due largely to discomfort), *"all patients were satisfied with the device and preferred it to previous treatment modalities used."*
Madjar	Journal of Urology - American Urological Association	92	0.04	Madjar reported that in the first phase of his two-part study, 47 subjects had a total of 14 UTIs in 357 subject-months (3.9% incidence) and all resolved with oral antibiotics.
Schurch	British Journal of Urology	18	Not Reported	Early study suffered from poor transition of a new technology to clinical practice and product quality issues.
Nativ	American Society for Artificial Internal Organs	17	0.03	Nativ reported that 14 evaluable subjects had a total of 3 UTIs in 118 subject-months (0.025% incidence). Interestingly, 2 subjects recovered bladder function after prolonged inFlow use (as did 8 subjects in other studies, total 10/228=4.4%).
Totals/Average		228	0.02**	207 unique subjects (Madjar studies were continuous for same cohort)

* UTI rate was not a prospective measure in the studies cited. This table is based on a retrospective analysis of studies reporting UTI rates.
** The five studies reporting UTI rates reported a total of 29 UTIs in 1,326 subject-months.

Mazouni C; Karsenty G; Bladou F; Serment G. *Urethral device in women with chronic urinary retention: an alternative to self-catheterization?* Eur J Obstet Gynecol Reprod Biol 2004; 115(1): 80-84
DOI: 10.1016/j.ejogrb.2003.10.031

Mazouni et al utilized inclusion and exclusion criteria similar to that in the pivotal trial and showed similar results. In a study of 60 subjects with chronic urinary retention, median age of 61.9 years old (range 40–89), Mazouni found the inFlow to be effective in emptying the bladder, had few significant complications and was a good solution for many users, but that a high percentage of subjects discontinued use.

The following is excerpted from the published report of this study:

"The mean maximal peak flow measured after 1 month was 14 ml/s (range 7–18). The post-voiding residual (PVR) volume was 15 ml (range 0–40). The incidence of urinary infection was 3.3%. (This compares to) a reported rate of 12% of urinary infection after 5 years of clean intermittent catheterization.

The abandonment of the prosthesis was noted in 50% (30/60) of cases within the first 15 days after implantation. The patient was free to stop treatment at any time. The insert was either removed at the clinic or by the patient herself. At the end of the procedure, 30 patients were using the In-Flow™ prosthesis with successful bladder emptying. The mean duration of the experience was 95 months (range 1–870). The longest experience with the device was 29 months, and in this case, the device has been changed 31 times."

As has occurred in other long-term studies of the inFlow, Mazouni reported several cases in which subjects recover voiding function despite a history of IDC and pre-study confirmation of this diagnosis via urodynamics:

"Spontaneous voiding function among the group of chronic urinary retention occurred without surgery in three cases at 10, 90 and 330 days, respectively, of using the device."

Study conclusions were as follows:

"The In-Flow™ prosthesis is an interesting alternative to classical treatment as it is associated with a low number of adverse effects. The complications were local and essentially caused by mechanical problems. In conclusion, the advantage of this prosthesis is the ease of insertion and removal, its low morbidity and the recovery of autonomy by the patient. This intraurethral prosthesis is an attractive, simple technique for use as an alternative to catheterization."

Lynch WJ, Testa GA, Bell D: *A Study to Determine Subjective and Objective Benefits of a Remote-Controlled Intra-Urethral Device for the Management of Female Acontractile Bladder.* Brit J Urol 2003; 92: 960-963.
DOI: 10.1111/j.1464-410x.2003.04525.

This non-comparative, investigator-sponsored study showed that a high rate of device acceptance can be achieved with patient education and active nursing support.

In a one-year study of 20 acontractile (IDC) bladder patients, Lynch et al. reported that 14 evaluable subjects had a total of 2 UTIs in 156 subject-months (0.01% incidence), almost no device-related dropout, 80% quality of life improvement per Wagner I-QOL scores, no negative tissue changes and concluded that "*the device provides an effective method of bladder drainage, with few side-effects and significant improvement in QoL."*

The following is excerpted from the published report of this study:

"Specific objectives were to show effective and complete bladder drainage and to evaluate any effect that the device has on the quality of life of the patients in the study. Twenty women were recruited for this study (mean age 64.5 years, range 37–87). All patients had no evidence of effective detrusor contraction during urodynamic assessment.

All patients had used the standard bladder drainage techniques; most had tried more than one of the alternatives. At the time of enrolment the techniques used were ISC in five, indwelling urethral catheter in eight and suprapubic catheterization in seven. All patients had expressed dissatisfaction with their particular method of bladder drainage, and were thus enrolled in this study.

The mean (range) flow rate was 10.7 (9–16) mL/s and the PVR 3 (0–17) mL. Two patients had a single UTI after the initial insertion of the Inflow; these responded to standard antibiotic therapy and did not recur. The patient who had had recurrent UTIs before inserting the Inflow interestingly had no further infections after establishing adequate bladder drainage.

The present small study shows that patients felt they had a significant improvement in their QoL when using the Inflow to effect their bladder drainage. If provided with appropriate support while the catheter was established even the mentally impaired can achieve effective and adequate bladder emptying. The side-effect profile is low and the risk of infection seems minimal."

Madjar S, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *Long-term follow-up of the inFlow™ intraurethral insert for the treatment of women with voiding dysfunction.* Eur Urol 2000; 38:161-166.

This study is a continuation of Madjar's 1999 study with the same cohort.

In the second part of this two-part study, 21 subjects were followed for more than a year with a mean follow-up time of 24.6 months, range 12-44 months (total 517 subject-months). Four episodes of symptomatic urinary tract infection were recorded, of them one upper urinary tract infection (4 UTIs/517 subject-months = 0.01% incidence). All patients who continued treatment were satisfied or very satisfied with the device.

Women who were sexually active prior to treatment did not have any difficulty with intercourse after treatment. All users were *"satisfied"* or *"very satisfied"* with the device and they preferred it to previous treatment modalities. Treatment success was associated with previous CIC, diagnosis of atonic bladder (now IDC), and sexual activity. Treatment failure was associated with no previous treatment for voiding difficulty, unknown etiology of voiding dysfunction, and pre-treatment bacteriuria. By multivariate analysis the only independent predictor of treatment failure was the absence of prior treatment for voiding difficulty.

Madjar's conclusions were as follows:

"*The new remote controlled intraurethral inFlow Catheter is useful for managing difficult voiding in women. The pump and valve assembly mimics normal urination by enabling a good stream of urine with complete bladder evacuation as well as continence between voids. The cost and incidence of symptomatic urinary tract infection are similar to those of clean intermittent catheterization. This device is safe and effective for women with difficult voiding."*

Madjar S, Sabo E, Halachmi S, Wald M, Issaq E, Moskovitz B, Beyar M, Nativ O: *A remote controlled intraurethral insert for artificial voiding - A new concept for treating women with voiding dysfunction.* J Urol 1999; 161:895-898.

This is the first study to show that a subset of women with chronic urinary retention requiring catheterization can successfully use the inFlow over a long period of time.

Subjects were 16 to 88 years old (mean age 56) with urinary retention due to “difficulty voiding.” The study demonstrated similar results to the pivotal study with respect to bladder emptying (post-void residual), complications, reasons for withdrawal and UTI rates.

In the first part (*n*=92) of this two-part study, 45 subjects discontinued device use <7 days due to discomfort or leakage and 47 subjects were followed with a mean follow-up time of 7.6 months, range 2-26 (total 357 subject-months). Causes of voiding dysfunction included previous pelvic surgery and external radiation (*n*=11), multiple sclerosis (*n*=9), diabetes (*n*=7), spinal injury (*n*=6), but was unknown in most cases (*n*=59). Unlike the pivotal trial, in which 99% of subjects were CIC users, this study included subjects whose previous treatments included indwelling catheter (*n*=21) and no treatment (*n*=16), as well as CIC (*n*=55).

All subjects received the inFlow device at the start of the study. Subjects returned for month follow-up, including urinalysis and culture, symptom assessment, satisfaction questionnaire and uroflow. The device was removed within 4 months (mean 7.1 days) in 45 cases (49%), due to local discomfort (*n*=25), urinary leakage (*n*=14), and difficulties with operation (*n*=6). The remaining 51% continued to use the device for a mean of 7.6 months. All remained dry and experienced complete bladder emptying. Twenty-two users (47%) had asymptomatic bacteriuria and 14 had a symptomatic urinary tract infection, all of which were successfully treated with oral antibiotics (14 UTIs/357 subject-months = 3.9% incidence).