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Management of Voiding Dysfunction After Female Neobladder Creation

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Abstract
Purpose of Review Functional complications after orthotopic neobladder urinary diversion (ONB), including urinary incontinence and urinary retention, present unique challenges. The purpose of this review is to outline contemporary treatment options for voiding dysfunction after ONB in females.
Recent Findings Meticulous surgical technique in the form of urethral nerve-sparing has been shown to play an important role in maintaining continence, as has sparing the uterus when possible. Data supporting the effectiveness of lifestyle measures, urethral bulking, pubovaginal slings, and transobturator slings in the treatment of urinary incontinence are widely variable and limited to case reports. Urinary retention is still most effectively managed with self-catheterization.
Summary Voiding dysfunction after ONB can be devastating. Recent advances focus on improving surgical techniques to decrease the risk of incontinence and retention, as postoperative management options are limited.

Keywords Orthotopic neobladder · Urinary incontinence · Urinary retention · Voiding dysfunction · Radical cystectomy · Female

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Introduction

Though urothelial cell carcinoma of the bladder is more prevalent in men, approximately one fourth of all new cases are diagnosed in women [1]. For several decades, radical cystectomy with urinary diversion has been considered the gold standard therapy for muscle invasive bladder cancer [2]. In females, this often includes an anterior pelvic exenteration with hysterectomy, bilateral salpingo-oophorectomy, anterior vaginal wall resection, and urethrectomy. In the 1980's, orthotopic neobladder urinary diversion (ONB) was introduced in men as an alternative to incontinent diversion [3–5]. Proponents of ONB cited advantages including spontaneous voiding, avoidance of an external ostomy, and improved body image.

Initially, fear of bladder cancer spreading to the female urethra was the main reason why urethral-sparing techniques were avoided in females. However, ONB has since been demonstrated to be oncologically safe in the properly selected patient [6, 7]. Approximately 12% of female high-grade muscle invasive bladder cancer patients undergoing radical cystectomy have urethral involvement [6]. It is our practice to avoid urethral sparing procedures in women with bladder neck or anterior vaginal wall involvement on preoperative assessment. Confirmation of negative bladder neck involvement on pre-operative cystoscopy and bladder neck biopsy or a negative intraoperative frozen section of the proximal urethral margin have been demonstrated to be a reasonable selection criterion for female ONB candidates [8•]. Beyond oncologic concerns are the functional challenges with creating ONB in women, including maintenance of continence and avoidance of urinary retention.

The purpose of this review is to outline the contemporary management of voiding dysfunction after female ONB

creation, specifically treatment of day and nighttime stress urinary incontinence (SUI) and hypercontinence.

Anatomic and Operative Considerations

After oncologic control with surgery, the next most important goal is optimizing functional outcomes. As our understanding of female urologic anatomy has progressed, so too has our ability to improve functional outcomes with ONB. Animal studies have shown that pudendal nerve stimulation results in a pressure increase in the distal urethra, while stimulation of the pelvic plexus results in a similar response in the proximal urethra [9]. Stasser et al. completely denervated a sheep urethra and noted marked degeneration of smooth muscle cells [10]. These studies provide evidence for the importance of preservation of the aforementioned nerves in the female continence mechanism. Bhatta Dhar et al. presented a large series of nerve-sparing radical cystectomies and ONB in females and stressed the importance of careful dissection in two particular areas: where the autonomic nerve fibers pass medial to the ureters and where they cross the uterine and vaginal arteries and the paravaginal/bladder neck regions [11]. Somatic nerve bundles originating from S2 to 4 have also been shown to run in close proximity to the inferior bladder pedicle, then course along the lateral vaginal wall to the urethra [12]. Thus, dissection of the vagina should be performed in the 2 and 10 o'clock positions (cancer-permitting), and the posterolateral (i.e., 4 and 8 o'clock) regions avoided to minimize nerve injury [11]. At our institution, we utilize a nerve-sparing technique where feasible, emphasizing meticulous dissection around the lateral vagina to minimize trauma to the nerves.

Another approach to improve functional outcomes is preservation of the uterus. Gross et al. demonstrated the benefits of preserving the uterus in a prospective analysis of urethral pressure profiles (UPP) in the female ONB population [13••]. Patients without a hysterectomy were more likely to be continent, have a longer functional urethra, have a higher urethral closing pressure at rest, and a higher continence product compared to hysterectomized patients. This supports the findings of a retrospective review of 49 female ONB patients where the only predictor of daytime incontinence was previous or concomitant hysterectomy [14]. The largest series to date assessing preoperative factors associated with gynecologic organ involvement found that women with any one of preoperative palpable mass, trigonal/bladder floor tumor location, or clinical lymphadenopathy were more likely to have gynecological organ involvement than women with none of these factors (28 vs. 10%) [15•]. Therefore, these factors may guide selection of organ preservation candidates. Interestingly, the authors did not find hysterectomy to be associated with catheterization or nighttime continence as in prior studies.

In select patients, organ preservation involves sparing the uterus, fallopian tube, ovaries, and vagina during radical cystectomy with ONB [16, 17•]. In a Japanese study of 30 patients, all had negative margins, and 80% were continent at a mean 36 months of follow-up [16]. Anatomically, leaving the vagina and uterus intact will provide support to the neobladder and reduce the risk of pouchocele formation and kinking of the neobladder-urethral angle, both of which may contribute to urinary retention [18]. Furthermore, minimizing dissection around the vagina should preserve the autonomic nerves coursing along the lateral vagina as outlined previously. Preservation of all internal female genitalia remains a controversial topic and in our practice is reserved for a very select group of patients. Though its purported enhancement of functional outcomes is desirable, the priority must be complete oncologic control. Until there is stronger data to support the oncologic safety of complete reproductive organ preservation, we would caution against its use in the majority of women undergoing radical cystectomy. We propose reserving its use for well-informed pre-menopausal patients without a preoperative palpable mass, non-trigonal/bladder floor tumor location, and no clinical lymphadenopathy who are accepting of a possible increased risk of recurrence.

Incontinence

Capturing the true prevalence of urinary incontinence after ONB is challenging due to a lack of standardized outcomes reporting. Reported rates of daytime incontinence range from 10 to 43% [11, 13••, 14, 18]. Even less well studied than the incidence of incontinence after ONB is its severity. Among post-operatively incontinent patients, one report determined 29% to have mild SUI (≤1 pad per day), 9% to have moderate SUI (2–4 pads per day), and 62% to have severe SUI (≥5 pads per day) [14]. Though unique in its aim to quantify the degree of incontinence, the retrospective nature of the study limited the authors to review of clinic notes rather than any standardized analysis of incontinence severity.

Prevention of incontinence in women undergoing ONB reconstruction is optimal and may be heavily reliant on appropriate patient selection. Rouanne et al. reported long-term outcomes (mean follow-up 5.7 years) on 41 female ONB patients [19•]. The only factor predictive of daytime incontinence postoperatively was age > 65 years (6/8 versus 2/23, $p = 0.001$). As noted previously, Anderson et al. found daytime incontinence to be associated with hysterectomy, and incontinence severity was associated with preoperative stress urinary incontinence (SUI) [14]. Thus, patients with age >65 years, previous or planned concomitant hysterectomy, and preoperative SUI should be warned about a higher possible incidence of daytime incontinence with an ONB. In general, we prefer ileal conduit or continent catheterizable diversion (e.g., *Indiana*

pouch) in women with these risk factors, especially if preoperative SUI is present.

A definitive diagnosis is imperative prior to pursuing management via one of the approaches in the urologists' limited armamentarium for treatment of post-ONB incontinence in women. The first step in diagnosis is ruling out other causes of leakage, including a neobladder vaginal fistula (NVF) or urinary retention with overflow incontinence. Suspicion of NVF should be raised if on physical examination urine leakage per vagina is noted without leakage from the meatus [20••]. Once SUI is confirmed, conservative measures used in the treatment of uncomplicated SUI should be applied, including pelvic floor physiotherapy and lifestyle modifications such as bladder emptying prior to physical activity and weight loss.

Urethral bulking agents serve as the least invasive surgical management option. Options include Deflux, Macroplastique, Coaptite, Contigen, and Durasphere. There is a paucity of contemporary data to support the efficacy of bulking agents, with complete continence rates ranging from 0 to 33% [20••, 21, 22, 23]. Bailey et al. described their experience with six patients treated with bulking agents [20••]. After a total of 12 injections, the authors reported that one woman was rendered dry, nine transiently improved, one immediately failed, and one developed NVF. Wilson et al. published results of 12 patients treated with 25 injections with a mean follow-up of 22.5 months [22]. At last follow-up, only 17% were dry, 33% had some improvement in average daily pad use, and 50% experienced no improvement. Lastly, Carmel et al. demonstrated improvement, but not complete continence, in all three women treated with bulking agents for SUI following successful NVF repair [23]. In general, bulking agents have limited efficacy and durability and are reserved for women who are not candidates for or wish to avoid the recovery and risks associated with more invasive options.

More invasive surgical options include pubovaginal slings (PVS), transobturator slings (TOS), and in intractable cases conversion to incontinent or continent catheterizable urinary diversion. PVS has long been the gold standard for treatment of intrinsic sphincter deficiency [24]. However, early reports of its use in post ONB urinary incontinence were poor with significant associated morbidity. In a series of four patients with postoperative incontinence, the two who underwent attempted retropubic pubovaginal sling developed enterocutaneous fistulas related to bowel injury during the retropubic dissection [25]. Both women ultimately underwent conversion to continent cutaneous diversion; however, one died from sepsis 4 months after this surgery. Subsequent procedures in two additional women avoided significant retropubic dissection using dermal grafts and infrapubic bone anchors, reportedly resulting in retention managed uneventfully with clean intermittent catheterization (CIC). These complications highlight the challenges with PVS placement in this population, as small intestine is typically densely adherent to the posterior aspect of the pubis. Thus, both small bowel and the neobladder are at significant risk of injury, with potentially devastating results. Bailey et al. placed four PVS slings (two cadaveric slings, two autologous slings) subperiosteally to avoid injury to the neobladder or small bowel in the retropubic space [20••]. However, only one patient achieved complete dryness, while the rest reported no improvement.

TOS represents another treatment option that limits risk of neobladder or bowel injury because it does not require retropubic dissection or needle passage. Like the PVS, reports of its use in the ONB population are limited to small case series with widely variable outcomes. Bailey et al. report the most contemporary series of four TOS surgeries (three synthetic slings and one autologous sling). Only one patient had improvement in her symptoms, while the other three failed to demonstrate any improvement [20••]. A report out of Egypt presented more promising outcomes [26]. Of the six women treated with TOS, four reported complete continence (one required CIC), one had improvement from 5 to 7 pads per day to one pad per day, and one had no change in her incontinence. Other case series [23, 27] have reported improvement or complete retention requiring CIC in individual women undergoing TOS. Given these mixed results, TOS is at best a moderately successful option for incontinence post ONB. The major advantage of the TOS versus the PVS is avoidance of the hostile retropubic space and potential injury to the ONB. When performed, we prefer non-synthetic materials to decrease the risk of erosion. In cases where symptoms are severe and not responsive to more conservative measures such as physical therapy or bulking agents, conversion to an incontinent diversion or continent catheterizable diversion may be appropriate, particularly in light of inconsistent and potentially dangerous results with sling surgery.

Nighttime incontinence affects more than 50% of women, although most of it is mild, and will often occur in the absence of daytime symptoms [14]. Many patients will have improvement in this symptom as the functional capacity of their neobladder increases with time [28]. Age >65 years is an important risk factor [18]. Postulated mechanisms for nocturnal incontinence include decreased sensation leading to nocturnal overdistension with subsequent failure of urethral closure mechanisms, physiologic diuresis, and rhabdosphincter relaxation during sleep [18]. Nerve sparing during radical cystectomy has been shown to be associated with improved rates of both daytime and nighttime incontinent, with nocturnal incontinence rates improving from 25% to 5% [3, 11, 29]. Unlike the numerous treatment options for daytime incontinence, management options for nighttime incontinence are limited. Lifestyle measures, including fluid reduction before sleep, are rarely successful on their own. The primary treatment modality is CIC prior to sleeping and potentially 1–3 times overnight.

Hypercontinence

Hypercontinence, or urinary retention, is a significantly more common problem amongst female ONB patients than in their male counterparts. Rates range from 0 to 53% in women compared to 0 to 33% in men, and hypercontinence is another reason to exercise caution in performing ONB in females [30]. Potential mechanisms for hypercontinence include angulation of the urethra, excess reservoir capacity, anastomotic stricture, pouchocele, and pelvic floor dyssynergia. Mikuma et al. studied the function of neobladders with urodynamics and determined successful voiders had a neobladder opening located at the most caudal portion and wide funneling of the bladder neck with voiding [31]. Thus, proper pelvic supports to maintain satisfactory orientation, as well as adequate pelvic floor relaxation are necessary to empty an ONB successfully.

Gross et al. eloquently studied pre- and postoperative urethral pressure profiles (UPP) in females undergoing ONB [13••]. Many patients with hypercontinence and an elevated PVR were initially able to void but developed retention after 3–6 months. Serial UPP measurements demonstrated increasing functional urethral length, increase in maximal urethral closing pressure at rest, and an increase in the continence product versus early postoperative UPP measurements. The mechanism for this may be recovery from neuropraxia that contributed to early post-operative denervation of the proximal urethra. Therefore, patients must be closely followed post-operatively as continence is a dynamic process. Cystourethroscopy may reveal a hypertonic urethra in these patients, and Gross et al. reported that two such patients were able to void spontaneously after transurethral incision of the proximal urethra. It is our routine practice to investigate all hypercontinent patients with cystourethroscopy to rule out an anastomotic stricture prior to embarking down any therapeutic routes.

Pouchoceles represent an interesting potential cause and effect of voiding dysfunction in female ONB. It has been hypothesized that pouchoceles most likely form as a consequence of poor voiding secondary to an inability to open the urethra. If parasympathetic innervation is preserved, sphincteric relaxation alone can allow urethral voiding without straining, circumventing the formation of a pouchocele [30]. Finley et al. described their results of pelvic organ prolapse repair in four post-ONB hypercontinent females and found a 50% success rate in reducing the need for CIC [30]. It is likely that pouchoceles most often form as a consequence of dysfunctional voiding, rather than being the cause. Documentation of obstructed voiding and organ prolapse with video fluoroscopic urodynamic assessment or dynamic pelvic MRI, if available, may be helpful in determining whether there is any potential functional benefit to surgical repair. In general, prolapse repair after ONB is a complex, invasive option with variable success rates for females who absolutely do not want to catheterize. These patients should be counseled about the possibility of continued need for CIC post-operatively or even conversion to an incontinent state.

Despite the advances made in our understanding of the pathophysiology of hypercontinence in the ONB setting, the mainstay of treatment remains CIC. The degree of retention is variable and the frequency of catheterization should be tailored accordingly to prevent overflow incontinence, urinary tract infections, stone formation, and renal dysfunction.

Conclusions

ONB in women after radical cystectomy is a viable option but may be associated with high rates of voiding dysfunction. Patient selection is critically important, generally favoring women who are younger. In addition, surgical technique plays an integral role in optimizing voiding function, with nerve-sparing and organ-preserving techniques having been shown to contribute to decreased incontinence and hypercontinence. Management of urinary incontinence represents a significant challenge and a thorough discussion should be held with patients about the limitations of currently available options. Surgical interventions are best performed at high volume centers with experience in complex pelvic surgery. Similarly, urinary retention can have a marked impact on quality of life after ONB. However, despite advances in our understanding of the underlying pathophysiology, treatment options beyond CIC are limited. Conversion to an incontinence or continent cutaneous diversion remains a last resort for both forms of voiding dysfunction. Research focusing on extensive organ preservation strategies to improve functional outcomes is promising, but one must always be mindful of the importance of oncologic control as the priority during radical cystectomy.

Compliance with Ethical Standards

Conflict of Interest Nathan Y. Hoy, Joshua A. Cohn, Casey G. Kowalik, and W. Stuart Reynolds each declare no potential conflicts of interest.

Melissa R. Kaufman reports money paid to her for teaching courses for Boston Scientific and Medtronic.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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