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Report from the Society for Women's Health Research

Expert Panel Recommendations on Lower Urinary Tract Health of Women Across Their Life Span

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Abstract

Urologic and kidney problems are common in women across their life span and affect their daily life, including physical activity, sexual relations, social life, and future health. Urological health in women is still understudied and the underlying mechanisms of female urological dysfunctions are not fully understood. The Society for Women's Health Research (SWHR®) recognized the need to have a roundtable discussion where researchers and clinicians would define the current state of knowledge, gaps, and recommendations for future research directions to transform women's urological health. This report summarizes the discussions, which focused on epidemiology, clinical presentation, basic science, prevention strategies, and efficacy of current therapies. Experts around the table agreed on a set of research, education, and policy recommendations that have the potential to dramatically increase awareness and improve women's urological health at all stages of life.

Keywords: urology, bladder, incontinence, LUTS, women's health

Introduction

Urologic problems are common in women (Table 1) and they affect their daily life, including physical activity, sexual relations, social life, and future health.[1–3] Multiple milestones during a woman's lifetime from infancy to old age can have an impact on their urological health, but little is known about urological changes during transition stages.

The Society for Women's Health Research (SWHR®) convened an interdisciplinary panel of experts (Table 2) to address the current state of research and to determine the most pertinent research priorities on October 28–29, 2014, in Washington, D.C. SWHR has advocated for women's health for over two decades through science, policy, and education. SWHR recognizes the need to have researchers and clinicians bring their diverse perspectives to define the current state of research, knowledge gaps, and provide recommendations *via* its roundtable meetings.

Seventeen participants were assigned to one of four subgroups according to their expertise and research interests (Table 2). Participants reviewed recent literature to examine and summarize key urological issues to set a framework for

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Table 1. Facts on Urologic Conditions in Women

53% of women will have at least one UTI during their lifetime.
24% of women, between the ages of 18–44, have UI.
Greater than 3 million American women are estimated to have IC/PBS.
About 5% of women will have at least one kidney stone by the age of 70.
Bladder cancer is the 10th most prevalent cancer in women, as of 2007.
Renal cell carcinoma is the 8th most common cancer in women, as of 2008.
Direct care for UI in 2000 costs $452.8 million for women (compared with 10.3 million in men).
Twenty-five to 44% women experience recurrent UTI annually.
In every racial group, women are 25–50% as likely as men to develop bladder cancer.
Three percent experience 3 or more recurrent UTIs within 6 months of their initial infection.

the roundtable discussion. A representative from each subtopic presented their collective perspectives. In this report, we summarize the presentations and discussions, including key knowledge gaps and panel recommendations, for advancing research on women's urological health.

Epidemiology and Clinical Presentation of Urologic Diseases Across the Life Span

Pediatric population

Urological health problems can begin early in childhood. These problems include increased urinary frequency and urgency (the strong sensation to void that cannot be deferred), urinary incontinence (UI; defined as involuntary loss of urine) after toilet training, nocturnal enuresis, urinary tract infections (UTIs), and bladder and pelvic pain. Children progress to urinary continence over a period of 5–7 years.[4] However, sex differences in toileting emerge by the age of 5, with girls reporting less bedwetting, but more daytime UI, than boys.[5] Childhood lower urinary tract symptoms (LUTSs) may be predictive of adult overactive bladder syndrome (OAB), which is defined as the uninhibited contraction of the bladder detected during urodynamics, which results in a constellation of symptoms, including urinary urgency with or without incontinence, urinary frequency, and nocturia.[6,7]

Comorbid conditions in girls include increased constipation,[8] elevated body–mass index (BMI),[9,10] forced or voluntary holding of urine, inadequate water intake, or consumption of dietary irritants. Stool holding and poor dietary choices at home and school lead to constipation and increased fecal loading in children, which is associated with OAB, UI, UTIs, and bedwetting.[8,11] Furthermore, constipated girls aged 8 to 18 years have significantly higher obesity rates.[12] The relationship of obesity and constipation with UI and bedwetting is a concern as the

Table 2. Society for Women's Health Research Urologic Health in Women Roundtable Participant List and Their Affiliations

A. Epidemiology of urologic diseases[a]
1. Cara Tannenbaum, MD, Professor, University of Montreal School of Medicine
2. Leslee Subak, MD, Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, Department of Urology, Department of Epidemiology and Biostatistics, University of California, San Francisco
3. Roger Dmochowski, MD, Professor, Department of Urology, Vanderbilt University

B. Clinical presentation of urologic diseases
1. Candace Parker-Autry, MD, Assistant Professor, Department of Obstetrics-Gynecology, Wake Forest School of Medicine
2. Clare Close, MD, Pediatric Urology, Close Pediatric Urology
3. Stephanie Kielb, MD, Associate Professor, Department of Urology, Northwestern University
4. George Kuchel, MD, Professor, Department of Geriatrics and Gerontology, University of Connecticut
5. Elizabeth Mueller, MD, Associate Professor, Department of Urology and Obstertics-Gynecology, Loyola University

C. Biological basis of urologic disease
1. Alan J. Wolfe, PhD, Professor, Department of Microbiology and Immunology, Loyola University
2. George Kuchel, MD, Professor, Department of Geriatrics and Gerontology, University of Connecticut
3. Michael DiSanto, PhD, Associate Professor, Department of Urology Research, Cooper Medical School, Rowan University
4. Toby Chai, MD, Professor, Department of Urology, Yale School of Medicine
5. Margot Damaser, PhD, Professor, Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic and Louis Stokes Cleveland VA Medical Center

D. Prevention and therapeutic strategies for urologic diseases
1. Matthew Fraser, PhD, Associate Professor, Department of Urology, Duke University
2. James Ashton-Miller, PhD, Professor, Department of Biomechanical Engineering, Department of Internal Medicine, University of Michigan
3. Margot Damaser, PhD, Professor, Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic and Louis Stokes Cleveland VA Medical Center
4. Cindy Amundsen, MD, Associate Professor, Department of Urology, Duke University

Participants were assigned to either one or two topic areas and were charged to examine knowledge gaps in their assigned topic area.
[a]Heidi S. Harvie, MD, MSCE, University of Pennsylvania, Philadelphia, participated in the conference calls before the Roundtable, but was unable to attend the roundtable meeting.

effects of these conditions on urologic health in women during later years are unknown.

Reproductive years

The prevalence of LUTSs in women increases throughout their reproductive years. Many lifelong behaviors become established during the teenage and early adult years, which makes this an ideal time for intervention to prevent poor bladder and dietary habits that could eventually lead to LUTSs.[5,10,12,13] The most common LUTS at this age is UI, including stress urinary incontinence (SUI), urgency urinary incontinence (UUI), and mixed urinary incontinence (MUI).[6] SUI is defined as involuntary urine leakage on physical exertion (exercise, coughing, sneezing). UUI is loss of urine with urgency. Finally, MUI is the occurrence of both SUI and UUI.

UI symptoms may begin early in the reproductive years. In 2011, 41% of young female athletes (median age of 22) reported having at least one episode of SUI during high impact activities.[14,15] Approximately 25% of women under age 40 report SUI during physical activity.[16] Of working women between ages 18–60, 37% reported urine leakage during the previous 30 days; 44% reported leakage at least once monthly during work hours; 21% reported weekly incontinence; and 8% reported daily incontinence or more.[17] More than 88% of these women reported a negative impact on concentration, physical activity levels, self-confidence, and ability to complete their work without requiring interruption.[14,15] UI symptoms are stigmatizing–90% of women with UI never discuss their UI symptoms with their healthcare providers.[14,15]

Pregnancy and vaginal delivery are prevalent comorbid conditions that may impact UI onset. Most women become sexually active in their reproductive years and subsequently experience pregnancy and childbirth, which are known risk factors for the development of LUTSs. After the first pregnancy, the odds of having SUI increased by 2.7-fold; up to a fourfold increased risk with 5 or more pregnancies.[18] During vaginal delivery, the pelvic floor muscles stretch to accommodate passage of the fetus under significant abdominal pressure. Consequently, innervation and connective tissue support of the bladder and urethra can be damaged.

While vaginal delivery increased the risk of SUI, cesarean delivery was not protective against developing UI. In fact, the risk of developing severe SUI and UUI was equivalent regardless of the mode of birth.[19,20] However, age at first delivery was associated with risk of UI. Women who delivered their first baby after the age of 30 had an increased risk of severe UI later in life and required more surgical interventions than those who delivered when they were younger.[21]

Postpartum development of UI is experienced by up to 30% of women.[22] Pelvic floor muscle exercises done using repetitions and sets have been shown to decrease incidence and severity of UI when performed during pregnancy and after delivery.[23,24] However, often UI symptoms recur later in life as increasing age is the predominant risk factor for onset of UI symptoms.

Obesity is a common risk factor for LUTSs. Two very large studies (Nurses Health Study and British Birth Cohort) showed that women with BMI >30 kg/m^2 had a 3.1-fold increased risk of severe UI compared with women with a BMI <25 kg/m^2.[25,26] Targeting weight loss in the PRIDE study showed that an 8% reduction in weight resulted in 47% decrease in UI episodes.[27] However, the cause–effect relationship between obesity and LUTSs has yet to be well defined.

The role of environmental factors such as diet is growing in importance in investigations of behavioral modifications for treatment or prevention of LUTS. In a prospective cohort study of 7046 community-dwelling women, increased smoking, intake of carbonated drinks, and obesity had significant associations with OAB with urgency incontinence, whereas dietary intake of vitamin D and calcium was seen as protective.[28]

Besides obesity and diet, other modifiable risk factors and comorbidities for UI included smoking, diabetes, constipation, stroke, hysterectomy, poor overall health, and chronic obstructive pulmonary disease.[29–36] Several of these factors individually increased the risk of UI by 30%–70%. Medications that interfere with cerebral processing of bladder function and/or have cholinergic effects on the smooth muscles, such as antidepressants, antipsychotic, and sleep medications, can exacerbate UI.[37]

Women of reproductive age also have a significant risk of UTI. The National Ambulatory Care Survey reported almost 30 million physician office visits for UTI from 2002 to 2007 (6-year count), with women over 45 accounting for over 26 million (>87%; 60% over 55 years old) of those visits.[38] Hospitalization rates for UTI in women over 65 were 4–45 times higher than for younger women. However, the epidemiology and treatment of UTIs are complicated due to the lack of objective diagnostic measures, including variations in collection (clean catch versus catheterized), lack of routine cultures to confirm diagnosis, nonspecific symptoms, and lack of guidelines on the use of antibiotics.

New evidence showed that urine is not sterile, highlighting our lack of understanding of the roles of asymptomatic versus symptomatic bacteria.[39–51] In addition, the definition of recurrent infections is debatable, further leading to either lack of appropriate treatment or mistreatment.

The prevalence of bladder pain syndrome (BPS) among women (3.8%) was as high as other painful conditions, such as migraine (2.1%), asthma (3.7%), and back pain (4.1%),[52] and was much more prevalent in women than men.[53] Women with bladder pain also had chronic pelvic pain. Women with BPS less than 30 years of age are more likely to experience urinary urgency, frequency, dysuria, dyspareunia, and pain in their external genitalia than older women who were more likely to experience nocturia, UI, and Hunner's ulcer disease.[54] While we understand the impact BPS has on women, an improved understanding of the etiology is needed to develop targeted and effective therapies.

Menopause and aging

Menopause is associated with higher risk of recurrent UTI, UI, LUTSs, and OAB, among other conditions. In addition, there is limited understanding of whether hormones affect urological function and, if so, the underlying mechanism(s).[55–57] For instance, 70% of women reported onset of UI at the onset of menopause,[55,56] but epidemiological studies that controlled for age suggested the effect might be driven by aging and not menopause specifically.

Geriatric population

UI is particularly prevalent in the geriatric population and has a major impact on quality of life.[57,58] Among women over

age 65, nearly 50% of community-dwelling women, 50% of female acute care patients, and over 70% of long-term care patients have UI.[59] In a Canadian study, UI increased the sense of loneliness in seniors from 38% without to 53% with UI.[60]

Beyond the psychosocial issues, elderly women with UI are at increased risk for falling and resultant bone fractures due to increased trips to the bathroom. For example, a self-reported study of over 6,000 community-dwelling women in the United States with mean age of 78.5 showed that 55% of women had fallen within the last 3 years and 8.5% had sustained fractures as a result of their fall.[61] Among the women who fell, 25% had weekly UUI, 19% experienced SUI, and 12% had mixed UI. Urgency (but not stress) UI was found to be independently associated with falls and fractures, increasing the risk by 26% and 34%, respectively, likely due to the increased urgency with which women with UI feel the need to get to the bathroom.[61]

Underactive bladder (UAB) and incomplete bladder emptying are associated with aging and are defined by either a prolonged time to empty the bladder or the inability to void completely.[62] UAB is increasingly being recognized as a cause of LUTSs, but has been an under-researched area.

Biological Basis of Urologic Diseases in Women

Function and dysfunction of the lower urinary tract

The primary functions of the lower urinary tract (LUT) are storage of urine (bladder relaxed and urethra contracted), emptying the bladder (bladder contracts and urethra relaxes), and protecting the LUT and kidney from damage due to high pressures or uropathogens. Neural control of LUT function is complex, involving both autonomic and somatic nervous systems, central and peripheral nervous systems, autonomous and volitional control, and is also affected by other psychological factors such as stress, anxiety, emotion, cognitive function, and executive function. Normal urinary storage and bladder emptying rely on proper function and integration of all these components, as well as pelvic structures supporting proper LUT position. The mechanisms of integration of all these factors are not known.

LUT dysfunction can be divided into pathologies of storage and voiding, which result in incontinence or incomplete emptying, respectively. Pathologies of storage include OAB, SUI, and UUI, while UAB is a pathology of voiding. OAB can result from dysfunction of cortical control centers, loss of inhibitory mechanisms within the detrusor muscle, or other dysfunctions of the neuromuscular system.[63–65] A correlation between inflammation and both OAB and interstitial cystitis (IC)/painful bladder syndrome (PBS) has been reported.[66,67] Biomarker studies may help explain mechanistic etiologies, thereby resulting in novel targets for therapeutic development, or serve to identify etiology-specific subgroups of symptom-based diagnoses to enable investigation of them as separate entities.

Among other causes, SUI can result from injury to urethral nerves, muscles, and connective tissue during childbirth,[19,68] a shift in position of the urethra due to insufficient support,[69] or loss of elastin and muscle density with aging or excessive straining or coughing.[70]

UAB results from a loss of detrusor muscle contractile power during voiding, decreased neural drive from the brain, and/or failure of relaxation of the pelvic floor or external urethral sphincter (EUS), among other etiologies.[71,72] Currently, the mechanistic pathways leading to LUT dysfunction are not well delineated, thus current therapies treat symptoms, but not the biological cause, of dysfunction.

Weakness or damage to the pelvic floor support of the pelvic organs, including the bladder, can result in a descent of these organs within the pelvis and in extreme cases through the pelvis. This condition, pelvic organ prolapse (POP), often occurs together with SUI and fecal incontinence, together collectively known as the female pelvic floor disorders (FPFDs). Female FPFDs are highly correlated with childbirth, but often do not occur until years or decades later, suggesting an interaction with age-related changes. Comorbidities, such as obesity, chronic cough, and diabetes, are also implicated in FPFDs.[19,73–75]

Genetic influences may provide potential explanation of why some women develop POP without undergoing pregnancy or vaginal delivery and other women never get POP, despite multiple vaginal deliveries.[76,77] The mechanisms of interplay of different contributing factors are not known; thus, current treatments for FPFDs, particularly POP, are based primarily on surgical correction of the anatomical problem and have significant risk of complications.[16,78] More research into causes of FPFDs is required to facilitate development of pathophysiology-based therapies, which could potentially constitute cures rather than symptomatic relief.

Female urinary microbiome

The female bladder contains bacteria that are typically not cultured by routine clinical laboratory techniques.[46,47,51] Preliminary data now suggest that the normal female urinary flora–the female urinary *microbiota* (FUM)–may have a role in modulating the risk of UTI or other urological conditions.[39–41,43,45,48,79] One pilot study reported that up to 75% of women with OAB have detectable bacteria in their urine and further that different FUM signatures are associated with OAB.[79] Together, these preliminary results may support FUM signatures as a diagnostic tool to improve treatment and/or prevent disease by identifying women at risk of LUT dysfunction[48] or by preserving or correcting FUM by probiotic usage.

Effects of aging

The prevalence and incidence of most urological conditions increase with age, but it is unclear whether this is a causal relationship. While normally the LUT is considered to be a behavioral system under voluntary control, there is no perfect correlation of LUT dysfunction with cognitive decline or other comorbidities, suggesting that urological dysfunction is not inevitable with aging.[80]

Studying the relationship between aging and development of urological conditions has primarily been done in rodent animal models. Proper models are key, and simply ovariectomizing young adult animals should not be considered a model for postmenopausal women, as these models do not incorporate age-related changes that normally accompany this event. Thus, when choosing an aging model, it is imperative to consider the normal aging process and to avoid obfuscating an induced pathology with normal aging.

Well-defined knockout animal models that partially mimic frailty, obesity, diabetes, sarcopenia, and osteoporosis can be

useful in defining the molecular basis of human disease. For example, animal models that study the biological pathways involved in senescence as a consequence of aging have shed light on the roles of proinflammatory senescent phenotypes, oxidative stress, telomerase, p53, and mTOR.[81] Importantly, there remains a need for well-characterized genitourinary tissues from older women and men that could be used to address primary research questions and human translatability of animal models as the human diseases that animal researchers attempt to model are still not well defined.

Animal models

Animal models are essential for understanding pathophysiological mechanisms, natural history, and for preclinical testing of therapeutic approaches, which simply cannot be done in humans. Animal models of male urologic conditions have been developed over 70 years; however, animal models for female urologic conditions have been utilized only for approximately 20 years, and many of these models face significant challenges because of differences between bi- and quadrupeds.[82] There exist particular needs to develop chronic animal models of female LUT dysfunction that better represent the multifactorial spectrum of clinical pathology (*i.e.*, mixed incontinence or FPFD). Although animal models will never replicate human diseases perfectly, they can help to dissect individual components of disease leading to highly valuable insights into mechanisms of disease and therapeutic development.

Current advances in genetic manipulation of animals, such as the CRISPR-*cas* system, are opening up possibilities to study humanized animals in ways that were not possible previously. In addition, genetic studies in humans can be complemented in animals in such a way that underlying causes of disease can be identified. For example, heritable factors may be identified using classical and novel genetic studies in humans (*e.g.*, GWAS), which can then be mutated in an animal for confirmation and analysis of the phenotype.

Gaps in our understanding of LUT function

To develop pathophysiologically based therapeutic options, a better understanding of contributions of the bladder and the urethra to LUT function is necessary. Historically, the approach has been to study the function of the entire LUT and to attribute changes in function as the result of changes in bladder function without considering the contribution of urethral function. While this is problematic for understanding both compartments of the LUT, studies that have been designed to study each compartment in isolation have focused disproportionately on bladder function. For example, the mechanisms that allow the female urethra to be functionally competent are not well studied, leading to an insufficient understanding of the pathophysiologies that underlie outlet obstruction and SUI in women. Therefore, more research should be directed to urethral function.

Another major gap in basic knowledge is bladder sensory signaling. Recent studies suggest that the primary cause of LUTSs may be due to alterations in sensory processing, including disorders in the brain.[83] In addition, the urothelium that lines the bladder lumen has been suggested to act not only as a barrier but also as a sensory transducer of bladder filling, but the mechanisms of this putative role require further elucidation. Nonetheless, the bladder mucosa and the lamina propria have been suggested to be important functional centers of the bladder.[84] The protective role of estrogen on the urothelium against UTIs and bladder cancer has been suggested, but is not fully understood,[85,86] similar to the role of reproductive hormones in LUT function and dysfunction.

Much research has been devoted to understanding the regulation of contraction and relaxation of the detrusor or urethral smooth muscle by direct neural regulation.[87] By understanding the intracellular mechanisms of smooth muscle contraction and regulation, we will improve our understanding of the excitation–contraction coupling event to develop new targets for novel therapeutic options.

Clinically, research on women who can void, despite not being able to generate sufficient detrusor contraction pressures, is of interest because it opens the possibility of more than one mechanism involved in voiding. Last, research is being conducted to develop alternatives to catheters for those patients who cannot void/empty their bladder, including bladder retraining, pharmacologic treatment, and neuromodulation.[88]

Prevention and Therapeutic Strategies for LUT Dysfunction

The last two decades have brought advances in treatments and therapies for female LUT dysfunction. However, improvement in therapies and development of prevention strategies require further research. A lack of precise delineation of pathophysiologic etiologies often leads to improper therapy selection with poor results. A precise understanding of etiologies will lead to effective prevention strategies.

Behavioral therapies

Behavioral therapies include behavior modification, bladder retraining, education, and self-help strategies. Reducing weight and increasing muscle tone improve continence and reduce the risk of LUTSs.[25,89,90] Management of fluid and caffeine intake, reduction of constipation, and training the bladder to hold longer (*i.e.*, bladder retraining) also have significant effects on incontinence.[64,90] Smoking cessation and proper treatment of chronic obstructive pulmonary disease (COPD) to reduce stress induced by coughing also reduce urine leakage.[31,91] Last, several medications can affect urological conditions. Sleeping aids can interfere with the signaling between the bladder and brain, resulting in leakage.[92] Behavioral modifications targeted at urological and gynecological hygiene (*e.g.*, postcoital voiding) may reduce the risk of UTI.[93,94]

Pelvic floor muscle training

Multiple studies have shown that women who used pelvic floor muscle training (PFMT) were 8 times more likely to report improvement in continence compared with controls.[95] A drawback and perhaps the reason for hesitation on the part of the public is that PFMT and other behavioral changes take time and effort–as many as 16 weeks for initial improvements–and a lifelong commitment to exercise. In addition, ineffective self-management can result in lack of improvement and frustration.[96] Therapies and prevention technologies that provide feedback (*i.e.*, biofeedback) can help women understand whether they are doing PFMT correctly.[96] Meta-analyses across more than 100 randomized control trials found inconsistent effects of almost all other therapies compared with PFMT.[78,97]

Table 3. Proposed Research Recommendations from SWHR's Urology Roundtable

Topic	*Specific recommendation*
Basic and Translational Science	Develop better animal models to study urologic health and disease across a woman's life span:
	To better reflect the coexisting diseases and outcomes as seen in patients
	Capture risk factors
	Identify clinical phenotypes and predictive biomarkers that allow for preclinical model development to define causes and treatment of disease
	To use in preclinical testing of novel therapeutics and prevention strategies
	Determine role of urinary microbiome in
	Normal bladder function throughout a woman's life span
	Cause and effects of disease states
	Future diagnostic tools and therapies
	Determine cellular and molecular mechanisms and genetic influences across a woman's life span to
	Understand lower urinary tract health in normal and disease states
	Establish impact of lifetime events or disease comorbidities on lower urinary tract function.
	Define disease subtypes for LUTSs.
	Improve knowledge of human lower urinary tract physiology to
	Develop better ways to clarify sensory and motor function in the urethra and bladder
	Understand the central neurological control of lower urinary tract
	Understand the role of cross talk between pelvic viscera
	Determine the role of biological sex in lower urinary tract health and disease in
	Host response to microbes
	Protection against carcinogenesis
	Determining sex differences in terms of contribution from urethral muscles toward urethral closure and the relative contributions of vascular, smooth, and striated muscles to urethral closure across the life span
	Develop ways to improve individual acceptance to lifestyle changes that have been shown to promote bladder health
	Develop prevention strategies for LUTSs
	Develop diagnostic markers for specific pathophysiology of LUTSs
Clinical	Increase the participation of women with multiple comorbidities in clinical trials, including the elderly and minorities
	Establish biobanks of tissues, blood, and urine across a woman's life span
	Explore novel therapies such as cell therapy and regenerative medicine
Therapies	Develop rational therapeutic approaches for LUTSs based on subtypes and biomarkers (personalized medicine)
	Examine differential response to same therapies by different people
	Examine synergistic effects of combination therapies
	Examine better ways to improve adherence to existing therapies

Based on existing knowledge gaps in the urology field, the discussions at the roundtable meeting led to the identification of key recommendations listed below.

LUTSs, lower urinary tract symptoms; SWHR, Society for Women's Health Research.

Passive devices: pessaries and urethral inserts

Vaginal pessaries have been used successfully to help reduce SUI.[92] Many women choose to use these devices because they can decide when they need to use them. For example, an athlete might decide to use her pessary while she participates in her athletic event, when her symptoms are acute, but remove the pessary for the rest of her daily life. Other intraurethral and intravaginal devices are popular and effective at strengthening the pelvic floor, thereby aiding continence.[90,92] These include weighted vaginal cones, vaginal spheres, and urethral inserts (*e.g.*, Femsoft®).[98] Clinical studies show that the use of these devices in combination with proper counseling and training was far more effective than their use alone.[90]

Pharmacologic treatments

Many pharmacological options exist for treating UUI and OAB, including anticholinergic (antimuscarinic) agents such as oxybutynin, tolterodine, trospium chloride, darifenacin, solifenacin, and ER fesoterodine.[99] These agents inhibit detrusor overactivity and may inhibit voiding ability. Anticholinergic agents are usually used in patients who do not improve with other more conservative treatments because of their side effects and the relatively high discontinuation rates.[99] β_3-adrenergic agonists are a newer class of drugs, which act at the level of myogenic detrusor reflex (instead of the neurogenic reflex), inhibiting not only detrusor contractions but may also interfere with filling.[99] OnabotulinumtoxinA (Botox®) inhibits involuntary contractions of the detrusor and therefore leads to improved continence.[90]

More than 70% of patients report at least a 50% reduction in symptoms after treatment, suggesting that Botox is relatively effective.[92] However, there remain questions regarding the length and durability of the treatment, as well as the location of administration (*i.e.*, trigone vs. outside the trigone). Last, with Botox there remain questions about how much damage the toxin has on muscles, whether the toxin accumulates over the life span, or whether multiple concurrent uses (cosmetic and urologic, for instance) can have long-lasting effects that have not yet been observed.

Table 4. Proposed Education and Policy Recommendations from SWHR's Urology Roundtable

Topic	*Specific recommendations*
Education	Implement professional development for primary and secondary school educators regarding bladder health
	Promote urinary health education and outreach in schools with community partner engagement
	Increase cross talk between clinicians and basic scientists
	Increase patient literacy, knowledge, and engagement on urinary and pelvic floor health
	Educate medical students, primary care physicians, primary nurse practitioners, and pediatricians on urinary health
	Develop educational campaign tools for lay public on healthy bladder habit
	Collaborate with subspecialty groups in advocacy
Policy	Promote evidence-based guidelines in women's urologic health
	Encourage insurance companies and Center for Medicare and Medicaid Services to reimburse for behavioral therapies for LUTS
	Develop a US-based public toilet map, maybe as an app if nonexistent, in conjunction with green spaces
	Mandate building code changes to make more washrooms for women in all buildings in the United States
	Develop workplace recommendations to facilitate healthy bladder behavior
	Modify primary and secondary school schedules to allow healthy bladder behavior
	Increase availability and accessibility to public restrooms

There are currently very few or no pharmacological treatments for SUI or UAB. For example, bethanechol is a muscarinic agonist used to treat UAB,[72] but there is no level 1 evidence for the use of this agent. Because of this, treatment of UAB is primarily limited to bladder catheterization. SUI can be treated with α-adrenergic agonists (pseudoephedrine, phenylpropanolamine) that contract the bladder neck or SNRI antidepressants (duloxetine) that act centrally on the pudendal motor neuron, which contracts the EUS.[100] These agents may have serious side effects and should be considered carefully in a risk–benefit analysis.[100]

A number of options exist for treatment of IC/PBS, including oral pentosan polysulfate, which presumably restores the glycosaminoglycan layer, which has been described to be a protective layer over the apical urothelial cell. Antihistamines have also been used to prevent mast cell degranulation.[101,102] Antidepressants and opioid pain medicines are also administered to reduce the symptoms of IC/PBS.[102]

Neuromodulation

Neuromodulation of the sacral 3rd (S3) nerve can modulate the urinary reflex to benefit patients with UUI and idiopathic urinary retention. The precise mechanisms of action for S3 nerve stimulation are not understood. For example, it is thought that increased S3 (pudendal nerve) afferent activity blocks abnormal descending excitatory, promicturition reflexes that occur in patients with UUI.[88] However, S3 stimulation can also suppress an exaggerated guarding reflex in patients with urinary retention.[88] Proper understanding of the mechanism of therapeutic action of S3 could help identify patient subgroups who would respond better to different therapies. Irrespective of the method of action, neuromodulation is recommended as a third-line therapy.

The clinical data are not clear on the persistent effects of sacral nerve stimulation and suggest that there is only a short period during which the effects continue.[88] However, long-term effects are not understood, and whether neuromodulation results in neuroplasticity is not known. Current improvements in electric leads and generators make S3 more appealing to patients. Broader and longer randomized control trials are needed to understand how frequently, for how long, and whether booster sessions of neuromodulation are needed for effective long-term treatment. Additional basic research is needed to understand the exact mechanism of action. Additional research into other nerves, such as the dorsogenital and pudendal nerves, is also needed to develop as therapies for patients with LUTS.

Surgery for stress UI

Midurethral slings are the most commonly performed surgeries for SUI, resulting in improvement in SUI symptoms in more than 70% of subjects.[103] The midurethral sling is the most studied procedure for SUI, and many studies have shown durability, efficacy, and improvement of quality of life.[104] Although uncommon, when mesh complications such as urinary tract erosion occur or when chronic pain develops, these side effects can be difficult to manage.

Regenerative medicine

Urethral bulking is a minimally invasive option for women with SUI. However, treatments are not long lasting and need to be repeated periodically.[78] Regenerative medicine, which uses adult stem cells to repair and/or regenerate tissues and organs, may provide a more durable solution. Several clinical trials are showing improved outcomes with stem cells injected into the bladder or urethra of women with SUI.[105] Stem cells are thought to repair damaged tissue by differentiation and proliferation. They also secrete bioactive factors that induce innate repair mechanisms, suggesting application of regenerative pharmacotherapy for SUI.[105]

Electrostimulation therapies that seem to regenerate tissue damaged during childbirth are also currently being explored as a prevention strategy for UI.[106] While still in the early stages, regenerative medicine offers opportunities to improve treatment and to prevent further development of disease conditions.

Discussion and Recommendations

After a day of topical presentations and discussions, the entire group discussed the most important research recommendations emerging from the Roundtable. A summary of

the discussion specific to each area follows. The specific recommendations are listed in Table 3.

As a whole, the experts agreed that given the demonstrated effectiveness of incontinence treatment, research is needed on methods of increasing healthcare-seeking behavior for women with incontinence as well as implementation of successful prevention and treatment strategies that extend the reach of and optimize individual adherence to effective continence promotion programs. However, while many effective treatments are available, there exists a fundamental lack of understanding of pathophysiology underlying LUT dysfunction, resulting in nontargeted therapies. Physicians are only able to treat symptoms, but cannot correct pathophysiological causes. This shortcoming is combined with the generalized grouping of patients according to symptoms rather than disease mechanisms and results in relatively poor management and ineffective treatment.

Discussions concluded that it is important to understand normal function along with dysfunction to identify the root cause of a problem with the ultimate goal of preventing disease. Knowledge gaps in research have resulted from inadequate phenotype definitions of urinary dysfunction, insufficient data to determine what is normal and abnormal, and animal models that do not appropriately reflect human disease. Specific research recommendations address these limitations, including the need for clinicians to better define disease states so that animal models that more accurately reflect these human conditions and their etiology can be developed.

There is a need for better understanding of molecular, cellular, microbiome, and physiological mechanisms of normal and abnormal function and improved understanding of the role of biological sex in urological function. Additional work is needed to develop animal models that discriminate between different disease etiologies (in incontinence, for example) to properly assess the efficacy and safety of newly developed treatments. Last, a precise understanding of etiologic mechanisms can inform how to develop preventative treatment strategies in the future.

The expert panel also discussed emerging issues that (while not related to research) are equally important. These fell into either public education/outreach or policy/advocacy categories (Table 4). The recommendations are meant for a general audience, including researchers, clinicians, advocacy groups, and policy makers. Experts around the table agreed that not enough awareness exists about the real impact of urological conditions on women's health and that there is a need to disseminate this information to a wide range of audiences. Dissemination of information to women patients and their healthcare providers and insurance companies is needed to increase urological health literacy and greater adoption and reimbursement of prevention strategies. Key audiences are primary and secondary school educators, nurses, and administrators given the fact that so many of our bladder habits are established in the early years.

Practical evidence-based information for lay audiences such as location of public toilets or workplace recommendations that promote bladder health by increasing number/location of available toilets or building time for toilet breaks during work shifts can also have significant impact on improving women's health at large. The group also identified an opportunity for more collaboration across disciplines and with advocacy groups to develop evidence-based guidelines in women's urological health that could ultimately become part of every woman's health management.

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