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REVIEW ARTICLE

# The female urethra: urethral function throughout a woman's lifetime

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## Abstract

**Introduction and hypothesis** The objective of this narrative review is to describe changes in urethral function that occur during a woman's lifetime. Evaluation of urethral function includes measurements of urethral closure pressure, at rest and during stress, leak point pressure, and the detailed study of anatomical and histological changes of the urethral sphincteric mechanism.

**Methods** A literature search in MEDLINE, PubMed, and relevant journals from 1960 until 2020 was performed for articles dealing with urethral function and the impact of aging, pregnancy, and childbirth, female hormones, and menopausal transition on the urethral sphincteric mechanism. Longitudinal and cross-sectional epidemiological surveys, studies on histological changes in urethral anatomy during aging, and urodynamic data obtained at different points in a woman's lifetime, during pregnancy, after childbirth, as well as the effects of female hormones on urethral sphincter function are reviewed. Relevant studies presenting objective data are analyzed and briefly summarized.

**Results and conclusions** The findings lead one to conclude that a constitutional or genetic predisposition, aging, and senescence are the most prominent etiological factors in the development of urinary incontinence and other pelvic floor disorders. Vaginal childbirth dilates and may damage the compressed pelvic supportive tissues and is invariably associated with a decline in urethral sphincter function. Pregnancy, hormonal alterations, menopausal transition, weight gain, and obesity are at best of secondary influence on the pathology of lower urinary tract dysfunction. The decline of circulating estrogens during menopausal transition may play a role in the transition of fibroblasts to cellular senescence.

**Keywords** Aging · Female hormones · Pregnancy · Childbirth · Urethral function · Woman's lifetime

## Introduction

The entire urethra acts as the urinary sphincter in the female. Under normal conditions, during the filling phase of the micturition cycle, the intraluminal pressure within the urethra exceeds the bladder pressure over almost the entire urethral length. The intra-urethral pressure is defined as the fluid pressure needed to just open a closed and coapted urethra. The term "urethral pressure profilometry" denotes a recording of the intra-luminal pressure exerted by the urethral wall on a pressure measuring device as it is withdrawn through the urethra from the bladder to the external urethral meatus [1].

Urinary sphincteric function is maintained by:

- The closure forces of the urethral wall that ensure a watertight seal of the urethral lumen
- Adequate transmission of intra-abdominal pressure increases to the bladder neck and proximal urethra
- Intact neurological control of the lower urinary tract (LUT)

The objective of this narrative review is to describe the dynamic and histological changes in the urethral sphincteric structure that occur during a woman's lifetime and their impact on urethral function. Longitudinal and cross-sectional studies provide epidemiological evidence of a positive association between age and the prevalence of lower urinary tract symptoms (LUTS): hormonal alterations, menopausal transition, pregnancy, childbirth, and cellular senescence are all associated with changes in the urethral sphincteric mechanism, and eventually may contribute to urethral dysfunction in later life.

## Materials and methods

A literature search in MEDLINE, PubMed, and relevant journals in the English language from 1960 to 2022 was performed for articles using the keywords: urethral function, aging, female hormones, pregnancy and childbirth,

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menopausal transition, and woman's lifetime. Methods used to provide objective data of urethral function include: simultaneous urethrocystometry, i.e., simultaneously recording of urethral closure pressure profile (UCPP) in relation to intravesical pressure (Fig. 1), both at rest and during stress (e.g., coughing, Valsalva maneuver), pressure transmission ratio (PTR = Δ Pura/Δ Pves × 100%) and abdominal leak point pressure (ALPP) measurement. Longitudinal and cross-sectional epidemiological surveys on urinary incontinence and LUT dysfunction are included. Studies of histological and anatomical changes during a women's lifetime and their impact on urethral function are described. Linkage studies on connective tissue and genetics are also included.

Urethral function tests, introduced in the early 1960s, have contributed considerably to a better understanding of the physiology of urethral function and the pathophysiology of LUT disorders.

## Simultaneous urethrocystometry

Enhorning [2], using fluid-filled balloon catheters and an external pressure transducer, was the first to develop and describe a technique for simultaneously recording the intraurethral pressure in relation to intravesical pressure. Water perfusion catheters (WFCs) with their external strain gauge transducer, first described by Brown and Wickham [3], and the dual microtip transducer with two pressure transducers embedded 6 cm apart in the catheter [4]), are currently the two techniques most widely studied and have been most commonly used in clinical practice since the early 1970s [3–5]. Both water perfusion catheters and microtip pressure transducers have excellent or very good reproducibility with an acceptable intra-individual variation for each of these methods. The within-patient coefficients of variation (CV = SD/mean × 100%) of these recording techniques, as determined by different investigators, are to a certain extent comparable and vary between 6 and 16% [6–13]. During the last two decades, sophisticated investigational methods have been developed as alternatives to conventional UCPP measurements. These methods include T-doc air-filled catheters, a single use disposable catheter introduced in 2017 and at present the most widely used catheter in the USA [14–17], fiberoptic catheters [18, 19], retrograde infusion of sterile fluid in to the urethra (URP, Monitor™) [20], and urethral pressure reflectometry (URP) [21]. So far, the clinical relevance of these new techniques has not been sufficiently validated. They do not seem to give any better information about urethral function than the traditional UCPP techniques using constant water flow (WFC) or dual microtip-transducer catheters [15–21].

Simultaneous urethrocystometry at rest in young asymptomatic nulliparous volunteers performed according to a standardized methodology [4] shows considerable variations in UCPP recordings within one subject as well as between subjects of the same age [6, 7, 11, 22, 23]. Urethral pressure variations (UPV) of ± 20 cm $H^2O$ without urine leakage in the absence of abnormal detrusor activity can be observed in asymptomatic healthy women and may be considered a physiological phenomenon caused by changes in urethral smooth and striated muscle activity. They are significantly more often recorded in women with LUTS [23–25]. Numerous investigators caried out simultaneous urethrocystometry at rest under standardized conditions to compare cohorts of women with stress urinary incontinence (SUI) with continent asymptomatic women of the same age and parity. These studies all show that SUI women generally have lower mean values of continence parameters, maximum urethral closure pressure (MUCP) and functional urethral length (FUL), than

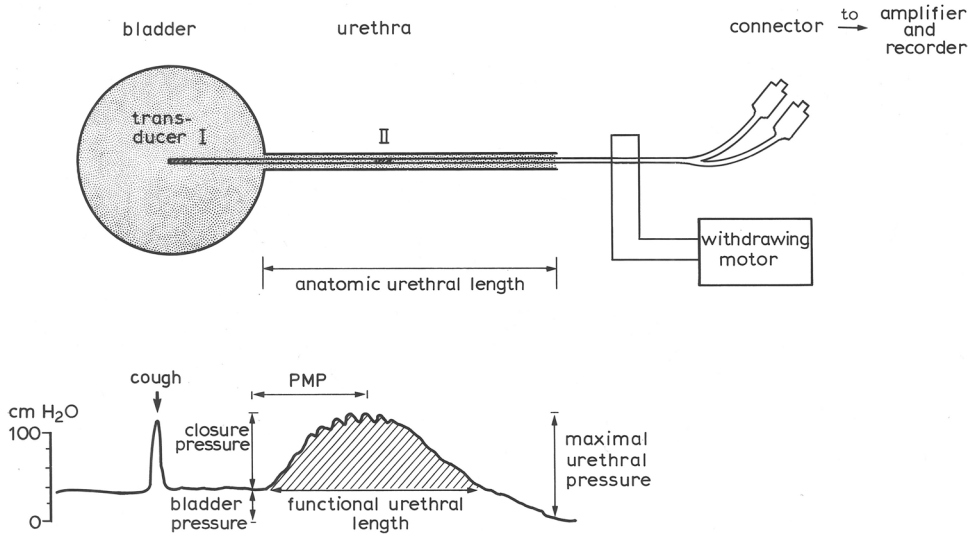


**Fig. 1** Schematic representation of the urethral closure pressure profile showing definitions of the variables measured. Continence variables: maximum urethral closure pressure (MUCP), functional urethral length. *PMP* distance from bladder neck to the point of Maximum Urethral pressure

matched controls. However, there is clearly a great overlap in UCPP variables between asymptomatic women and incontinent women. A clear cut-off value of UCPP to discriminate between continence and incontinence cannot be established [6, 26–31]. Lack of standardization of UCPP recordings such as recording technologies and methodological and patient characteristics render comparison of results between different studies impossible [6]. For good and accurate recording of urethral pressure changes in vivo the use of more than one urethral sensor is advocated [32, 33]. Simultaneous urethrocystometry is first and foremost a research tool for better understanding the pathophysiology of incontinence and other LUTS [1].

The term "urethral instability" denotes urine leakage due to spontaneous fall in urethral closure pressure in the absence of raised abdominal pressure or detrusor contraction [1, 25, 33]. This condition is relatively rare, but may be recognized as a cause of incontinence [34].

### Pressure transmission ratio

Dynamic UCPP recordings of the increase in urethral closure pressure during coughing and/or Valsalva in relation to the increase in bladder pressure define the pressure transmission ratio ($PTR = \Delta Pura/\Delta Pves \times 100\%$). In healthy, asymptomatic subjects the proximal two-thirds of the urethra lie within the abdominal cavity [2, 35–37]. An increase in intra-abdominal pressure will be almost equally transmitted to the bladder and proximal urethra. In the distal urethra, at the level where the urethra passes through the urogenital diaphragm, the magnitude of the urethral closure pressure rises during a cough is normally higher than the increase in bladder pressure owing to reflex contraction of the peri-urethral striated muscles [38–40]. In continent women this guarding reflex precedes the increase in bladder pressure by approximately 200 ms [2, 37, 40]. Consequently, abdominal pressure increases are not equally transmitted over the urethral length [41]. Bump et al. evaluated the validity of PTRs compared with a positive cough test. Using a cutoff of <90%, PTRs yielded a sensitivity of 97% and a specificity of 56% in predicting SUI [42]. Cundiff et al. determined the test–retest reproducibility of PTRs in a group of 242 stress continent women and SUI women and found PTRs to have a reasonable quantitative and qualitative reproducibility independent of cough intensity. When mean PTRs were stratified into below 90% and at least 90% categories, 83.5% of subjects had a test–retest concordance: $K = 0.671$ [43]. The high degree of individual variability in the resting urethral resistance, as well as individual variability in reflex contractility of pelvic floor muscles during stress limits the utility of PTRs to distinguish between women with and those without urethral incompetence [6, 37, 42].

### Abdominal leak-point pressure

Abdominal leak-point pressure (ALPP) is defined as the intravesical pressure at which urine leakage occurs because of increased intra-abdominal pressure in the absence of a detrusor contraction [44]. In an anatomically normal urethra with a competent internal and external sphincter mechanism increased intra-abdominal pressure does not cause urine leakage. Originally, ALPP was introduced for the assessment of urethral sphincter competence and urinary loss provoked by coughing and/or Valsalva was considered to be the gold standard for the clinical diagnosis of SUI. However, there is no agreed standard way of performing ALPP measurements such as bladder volume, catheter size, patient position, and zeroing of the external transducer [6, 45, 46]. ALPP and MUCP correlate modestly with each other and both are comparable in predicting incontinence severity [47]. Schick et al. in a group of 255 selected patients, found a significant relationship between MUCP values, urethral incompetence and urethral hypermobility [48]. Urine leakage with an intra-abdominal pressure increase <60 cm $H_2O$ and a MUCP ≤20 cm $H_2O$ is suggestive of intrinsic sphincter deficiency and is related to the severity of the condition, with a higher risk of failure from stress incontinence surgery [49, 50]. Delancey et al. have shown that MUCP and not urethral support is the factor most strongly associated with the diagnosis of SUI [51]. The clinical relevance of each of the urethral function tests is limited as they do not meet the criteria for a reliable diagnostic test, i.e., standardization of the procedure, reproducibility of the measurements, calculated parameters must have a high sensitivity and specificity with clear cutoff levels and no overlapping values, and calculated parameters must correlate with the outcome of treatment [6]. A large multicenter, randomized clinical trial performed in the USA, involving women with uncomplicated demonstrable SUI, has shown that standardized pre-operative office evaluation was not inferior to urodynamic testing for outcomes of treatment at 1 year [52].

## Results

### The impact of aging on the urethra

Numerous longitudinal and cross-sectional studies provide epidemiological evidence for a positive association between age and the prevalence LUTS [53–58]. Urodynamic investigations including UCPP in women of all age groups show that after the age of approximately 25 years the continence parameters MUCP and FUL decrease with increasing age. The decrease in MUCP is continuous and estimated to be within the range of a 15-cm $H_2O$ decrease per decade, in both nulliparous and multiparous women. This occurs similarly

in both continent and incontinent women [59]. Edwards and Malvern first described a negative linear correlation between the urethral closure pressure and age in asymptomatic women and proposed a formula for normal values of urethral closure pressure in relation to age: MUCP amplitude in cm $H_2O = 92$ – age [60]. Kapoor et al. in a study of nearly 9.000 women who underwent urodynamics for non-neurological referrals, calculated the normative data for MUCP = 116 − age and a decrease by 1 cm $H_2O$ for every year of age [31]. Except for a decrease in urethral length, no distinct additional decrease was observed for urethral pressure measurements in relation to menopause [2, 11, 29, 59].

### Histology

Morphological and histological studies of urethral and paraurethral tissue, from biopsies obtained during operative procedures and from cadavers, clearly demonstrate that the structure of the female urethra undergoes typical changes as a consequence of hormonal alterations and advancing age [61–65]. In women of reproductive age the urethral mucosa (urothelium) and the highly vascularized submucosa constitute a compressible and easily deformable layer that contributes approximately 30% to the intraluminal urethral pressure at rest [66]. Under compression from increased abdominal pressure and/or contraction of urethral and periurethral striated muscles this spongy structure, also referred to as "inner urethral softness," will coapt and ensure a watertight seal within the urethral lumen [67–69].

Cytological changes similar to those found in vaginal epithelial cells are observed in the urethral epithelium as a result of circulating estrogens during the menstrual cycle, from menarche to the menopausal transition. Postmenopausally, the multi-layered stratified squamous epithelium gradually changes to a single layer columnar epithelium with a decline of mucosal folds and urethral tissue perfusion [62, 69, 70]. The submucosa consists of loose areolar stroma in which a great number of arterio-venous anastomoses and thin-walled venous sinuses surrounding the urethral lumen may be observed. Berkow and Amboy [70] and Huisman [61] pointed out that the blood supply and the number of venous sinuses are excessive in relation to the metabolic activity of this tissue. The number of arteriovenous anastomoses declines postmenopausally and is gradually replaced by a preponderance of wide thin-walled venous sinuses (Fig. 2, transverse sections of mid-urethra premenopausally and postmenopausally) [62, 70].

### The urethral smooth muscle

The urethral smooth muscle layer forms a tough and compact tubular structure surrounding the urethral mucosa and submucosa and consists of relatively small smooth muscle bundles embedded in compact fibroelastic collagenous tissue. The more prominent inner longitudinal layer and the smaller outer circular layer surround the urethra for almost its entire length. The contribution of the smooth muscle component together with its binding fibro-elastic connective tissue to the resting urethral closure pressure varies according to different investigators and ranges from 30 to 80% [66, 71, 72]. The effect of age on urethral smooth muscle is still controversial. Most investigators have found no change in the urethral smooth muscle component with advancing age [72]. Clobes et al. noted a decrease in the density of the circular smooth muscle layer in older women compared with their findings in young women [73]. Semmelink et al. using histo-morphometric parameters observed hormonally induced age-independent atrophy of the smooth muscle in the lamina propria of the mucosa and in the longitudinal smooth muscle layer in postmenopausal women ($N = 37$, age range 18–82 years). According to these authors, age changes are at best of secondary influence on decreased MUCP seen with aging [74].

### The striated muscular component

The striated muscular component of the urethra consists of the intrinsic striated urethral and the extrinsic peri-urethral striated muscles. The intrinsic urethral striated muscle partially surrounds the urethral lumen in a horseshoe-like pattern over about 20% to 80% of the urethral length and contributes approximately 30% to the MUCP at rest (Fig. 3) [66]. The intrinsic urethral striated muscle is separated from the extrinsic periurethral striated muscles by endopelvic connective tissue [40, 75]. Anatomical and neurohistochemical studies have demonstrated morphological differences and differences in innervation between the urethral striated and the peri-urethral striated pelvic floor muscles. The small-diameter slow-twitch fibers of the urethral striated muscle are functionally capable of maintaining tone over prolonged periods without fatigue. The large-diameter fast-twitch and slow-twitch fibers of the pelvic floor striated musculature allow for rapid, forceful muscle contraction and thus seem ideally suited to increasing intraurethral resistance during sudden increases in intra-abdominal pressure during coughing and sneezing. This musculature enables voluntary interruption of micturition. These observations suggest different functional activities of these separate components [40, 75, 76].

Morphometric and histological studies of the female urethral striated muscle corroborate the clinical observations on the impact of age on urethral function. As age increases, the diameters of the muscle fibers show greater variation, whereas the number and density of urethral striated fibers decline. An average of 2–4% of striated fibers are lost per year [62–66]. The age-related changes in the smooth and striated urethral muscle may contribute to the high incidence of LUT disorders in the elderly population.

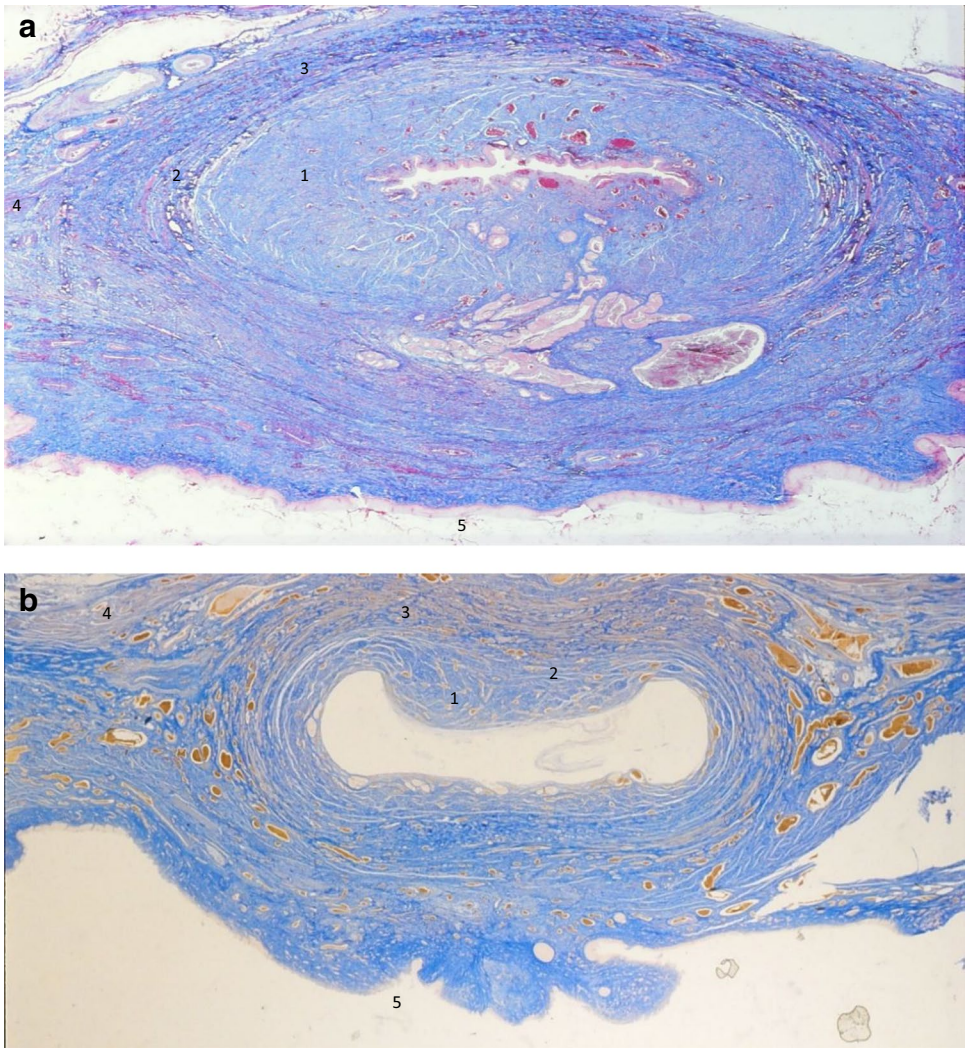


**Fig. 2** **a** Transverse section mid-urethra: pre-menopause azan stain. Magnification ×2.5 (presented at 42nd IUGA Annual meeting Vancouver 2017: abstract A-456). **b** Transverse section mid-urethra: postmenopause. Azan stain. Magnification ×2.5 (presented at 42nd IUGA Annual meeting Vancouver 2017. Abstract A-456). *1* Longitudinal urethral smooth muscle, *2* circular urethral smooth muscle, *3* intrinsic striated urethral muscle, *4* extrinsic periurethral striated muscle, *5* vaginal wall

The supportive connective tissue of the pelvic floor is a continuous interdependent sheet of endopelvic connective tissue. This "endopelvic fascia" supports the bladder base, the urethra and the pelvic organs. Fused with the anterior vaginal wall, the "endopelvic fascia" attaches laterally to the os pubis and arcus tendineus fascia pelvis and forms a hammock-like layer against which the urethra is compressed [38, 39, 76]. This connective tissue is a composite of collagen and elastin embedded in a non-fibrillar ground substance [77]. Ulmsten et al. compared the collagen content in biopsies from the skin and ligamentum rotundum of 7 women with a long history of SUI with that of 8 continent controls of comparable age and parity. The extractability of collagen in skin and ligamentum rotundum in both tissues was the same for both groups. The total concentration of hydroxyproline, a ubiquitous amino acid of collagen in skin from SUI women was 40% lower than that of controls. Similarly, for the ligamentum rotundum, hydroxy-proline concentration was 25% lower in the incontinent group [78]. These findings indicate that histological differences between women with SUI and asymptomatic controls may be associated with a genetic defect in the biochemical composition of their connective tissue. Jackson et al. has shown that genitourinary prolapse is associated with increased collagen turnover leading to a reduction in total collagen content and a decrease in collagen solubility [79]. Most studies on collagen metabolism indicate a genetic predisposition to abnormal extracellular matrix remodeling, which is modulated by reproductive hormones, mechanical stress, and aging. The question to what extent the alterations in connective tissue metabolism and fibroblasts are due to a genetic or an acquired defect is not yet elucidated. The changes in the metabolism of collagen increase with increasing age and may ultimately lead to a decline in connective tissue resilience and facilitate progression to pelvic floor disorders [80–85].

## Pregnancy, childbirth, and the urethra

Our knowledge of the impact of pregnancy and childbirth on urethral function stems mainly from retrospective studies

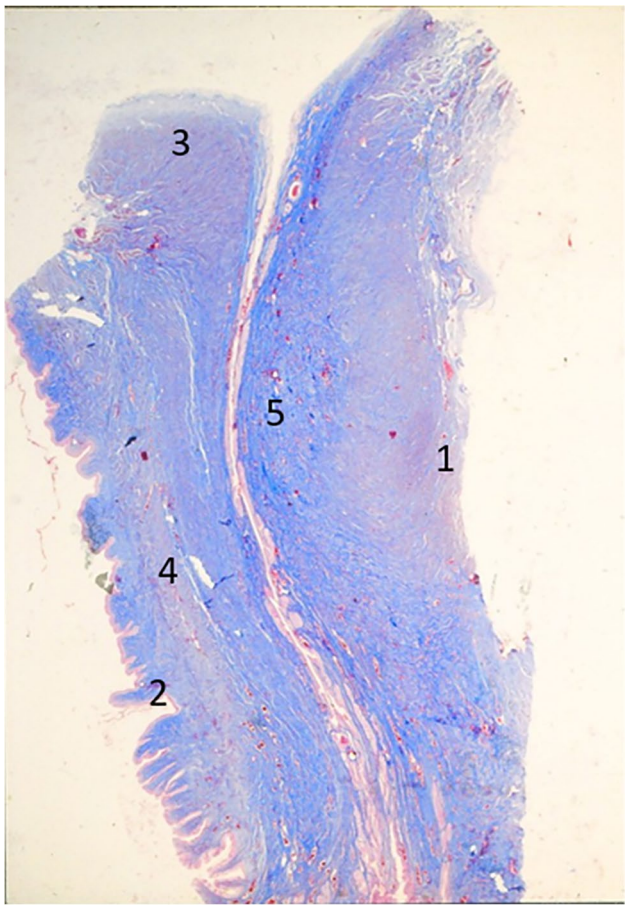


**Fig. 3** Longitudinal section female urethra: Azan stain. Magnification ×2.5 (presented at 42 IUGA Annual Meeting Vancouver 2017 Abstract A-456). *1* striated urethral muscle, *1* vaginal wall, *3* deep trigone, *4* endopelvic fascia, *5* urethral smooth muscle

and questionnaires. Longitudinal studies with objective quantitative data on bladder and urethral function during pregnancy and after childbirth are scarce. Two prospective studies assessed the effects of pregnancy and obstetrical variables on bladder function before and after childbirth. Winifred Francis published the first longitudinal prospective study, including cystometry and urethrocystography, of a cohort of 400 unselected pregnant women. Fifty-three percent of the primigravid and 85% of the multigravid women experienced SUI to some degree during pregnancy. Persistent severe incontinence after childbirth was observed in 6%, whereas another 23% admitted to occasional incontinence during coughing and sneezing. Francis concluded: "SUI rarely, if ever, appears for the first time after childbirth, if it had not occurred before or during pregnancy. Symptoms tend to resolve in puerperium, but in a small percentage UI persists or develops de novo after vaginal delivery" [86].

Chaliha et al. carried out a longitudinal study including 286 nulliparae with a singleton pregnancy. Dual-channel subtracted cystometry was performed in 286 women at 34 weeks' gestation. Twelve weeks after childbirth cystometry was repeated in 161 women. Antenatally, the authors observed a prevalence of SUI and detrusor instability of 9% and 8% respectively, and post-partum of 5% and 7% respectively. Neither pregnancy nor delivery resulted in any consistent effect on objective bladder function [87].

Few investigators have performed prospective studies using simultaneous urethrocystometry under standardized conditions to evaluate urethral function in normal pregnancies and in pregnancies complicated by urinary incontinence to evaluate the effect of pregnancy and childbirth on the urethral continence mechanism [88–91]. Except for a significant correlation between an increase in urethral length and increased 17-β-estradiol (4 mm: $p<0.001$), mean values of urethral continence parameters (FUL and MUCP) did not change significantly in the course of pregnancy. Mean values of MUCP, measured during pregnancy, were significantly decreased when compared with corresponding values recorded in asymptomatic nulligravid women of comparable age [89, 90]. No correlation between increased levels of progesterone and changes in MUCP could be demonstrated.

MUCP and FUL were significantly decreased 8 weeks post-partum when compared with early pregnancy values in all women who delivered vaginally (Fig. 4). These changes were not seen in women delivered by cesarean section performed before or early in labor [89, 91].

About 30% of primigravid women developed some degree of incontinence in their ongoing pregnancy. When compared with continent primigravid women, SUI manifested itself in those women who demonstrated, early in their first pregnancy, a low MUCP and defective transmission of intra-abdominal pressure rise (PTR) to the urethra in both supine and standing positions (Fig. 5).

There is circumstantial evidence that in pregnancy loss of strength with laxity of the pelvic floor connective tissue plays an important role in the pathophysiology of urinary incontinence (UI) and pelvic organ prolapse (POP). Landon et al. demonstrated that during pregnancy the mechanical properties of the connective tissue are altered. Pregnant fascia stretches to a much greater length when traction is applied but less force is required to produce disruption of the collagen fibers and tissue failure resulting in reduced tensile strength. Pregnant fascia is more elastic but also more easily damaged or ruptured than nonpregnant fascia [92]. UCPP measurements during pregnancy have shown that urethral length increased by approximately 4 mm as pregnancy progressed, whereas no correlation between urethral pressure variables and the rise in hormone levels could be demonstrated. These observations are in accordance with the findings by Landon et al. [92] and most probably represent a necessary physiological accommodation during pregnancy.

The urodynamic studies cited above, as well as detailed imaging techniques performed during pregnancy, do not

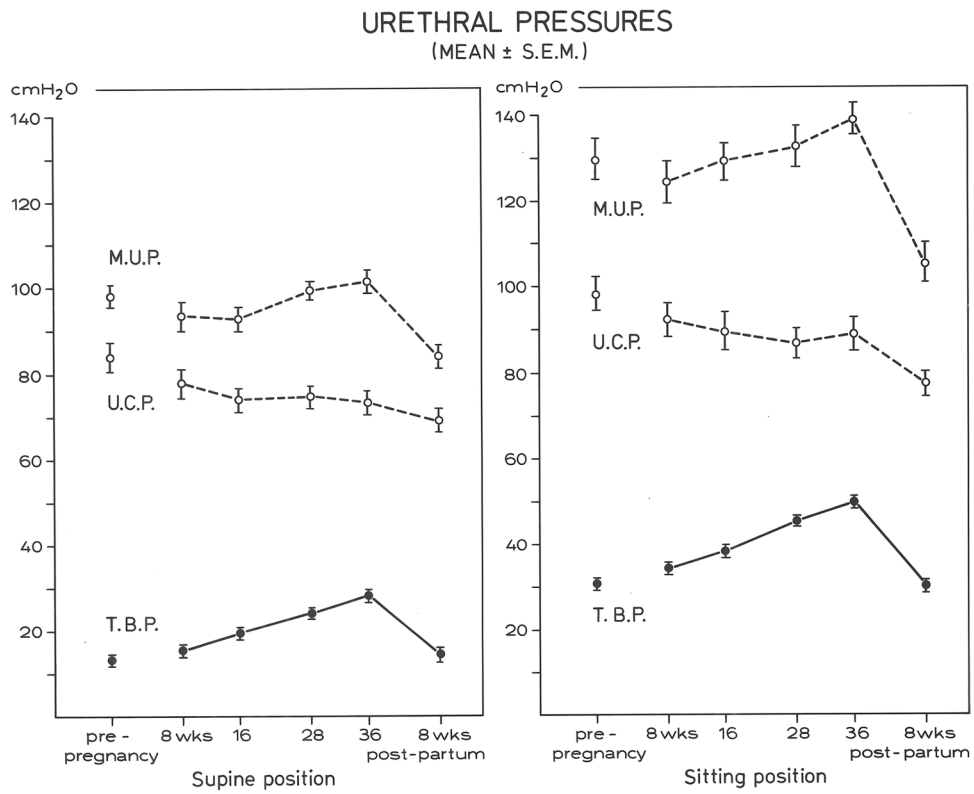


**Fig. 4** Mean values ± SEM of urethral pressure variables during pregnancy and at 8 weeks postpartum in the supine and sitting positions. Prepregnancy values obtained earlier in a group of nulliparous women are given for comparison. Values presented for the group of vaginal deliveries only (Am J Obstet Gynecology 1982:144)

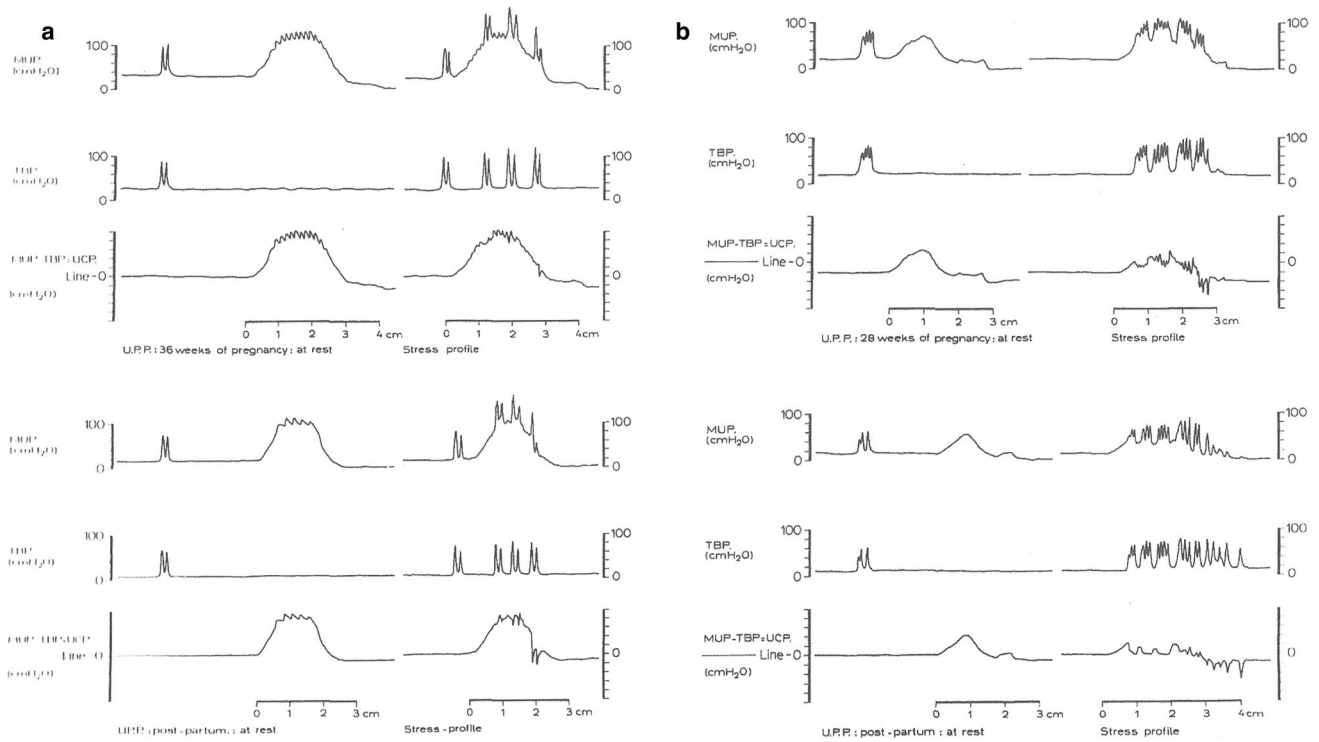


**Fig. 5** **a** Urethral closure pressure profile (UCPP) in a continent 1-gravid at 36 weeks of pregnancy and at 8 weeks post-partum. Supine position. **b** UCPP in a 1-gravid with stress urinary incontinence at 28 weeks of pregnancy and at 8 weeks post-partum. Supine position (Am J Obstet Gynecol 1982:144)

sufficiently explain the high incidence of SUI antenatally with recovery in most women after childbirth. The objective data on urethral function obtained during pregnancy, the results of biochemical studies on connective tissue, and the association of a high incidence of pelvic floor dysfunction amongst relatives, notably amongst identical twins, suggest that a constitutional predisposition, whether acquired or genetic, might have an important role in the development of pelvic floor disorders [85, 86, 89, 93].

Vaginal delivery further weakens the urethral sphincteric mechanism and the pelvic floor supportive structures [94–96]. In the majority of new mothers (80–90%) the traumatic and connective tissue changes are reversible and symptoms will resolve in the immediate post-partum period. In a minority, notably those with constitutional weak supportive tissue, incomplete tissue healing, and partial denervation may persist, eventually leading to permanent incontinence. These observations are in agreement with the findings of prospective longitudinal cohort studies including primigravid women, who answered validated questionnaires (ICS) after delivery, 3–6 months later and again 12 years later. Their results show that when SUI begins during the first pregnancy in approximately 30% of women, the risk of SUI symptoms 12 years later is significantly increased (OR: 4.5). Pre-existing obesity and an active stage of labor > 1 h were independently associated with persisting SUI 12 years after delivery [97, 98]. At older age, over 65 years, when the prevalence and severity of incontinence increase, the effects of parity as a risk factor disappear [99].

## Female hormones and the urethra

The presence of α- and β-estrogen receptors and progesterone receptors in the female urogenital tract suggests that alterations in hormone levels might play a role in both the structure and function of the urinary continence mechanism [100–102].

Numerous studies have assessed the effects of steroid hormones on the bladder and urethra, but few have examined the effects on LUT function in relation to the actual levels of circulating estrogens ($E_2$) and progesterone (P) [102, 103].

Recordings of UCPP in young asymptomatic women during their reproductive years with a normal menstrual cycle show that the mean values of urethral pressure measurements obtained during one menstrual cycle do not change systematically with hormonal alterations ($E_2$ and P) as determined during the menstrual cycle. Apart from a significant correlation between an increasing level of $E_2$ and increased urethral length (Kendall rank correlations FUL 0.34 and anatomical urethral length 0.30) and an increase in amplitude of vascular pulsations, no other correlations were detected. An effect of progesterone in the luteal phase of the menstrual cycle on the UCPP variables could not be demonstrated [103].

The decline of circulating $E_2$ at the time of the menopausal transition is associated with morphological changes in hormone-sensitive tissues of the LUT including thinning of the urothelium, a decrease in blood flow volume, a decrease in both quantity and quality of collagen and elasticity of connective tissue, muscle atrophy, and nerve degeneration (Fig. 2). These changes, called urogenital atrophy, may give rise to a wide range of LUTS including frequency, nocturia, urgency, urgency urinary incontinence (UUI), SUI, dysuria, vaginal soreness, and increased incidence of LUT infections. Not all climacteric women suffer these symptoms and the degree of discomfort differs between symptomatic women [104–108].

Epidemiological data, subdivided for different age groups, and prospective cohort studies carried out throughout the pre- and peri-menopausal years show a distinct peak in the prevalence of mild SUI and UUI at the time of menopause. After the final menstrual period, prevalence rates of SUI actually decrease until the age of 70–74, whereas the incidence of irritative LUTS increases with advancing age. Urogenital atrophy and age-related pathophysiological changes sufficiently explain the increase in irritative LUTS with advancing age [57, 105–108]. Although epidemiological studies suggest that menopausal transition is a major risk factor for the higher incidence of LUT and pelvic floor disorders, urodynamic studies show no distinct decrease in urethral pressure measurements in relation to menopause [2, 11, 29, 60, 61].

A large number of reviews have evaluated the role of estrogen administration, both local and systemic, in the management of LUT dysfunction in postmenopausal women.

The Cochrane Incontinence Review Group analyzed and summarized the effects of local and systemic estrogens for the treatment of stress, urgency, and mixed urinary incontinence [109].

Thirty-four randomized or quasi-randomized controlled trials, published before 2012, fulfilled the inclusion criteria: 18 investigated systemic estrogen administration, 17 local administration, and 1 trial investigated both local and systemic administration. The results of this data-based systematic review are in agreement with the findings in other reviews assessing the effects of hormones on LUT function. Almost all the reviews, which include randomized controlled trials and/or objective parameters, show that topical estrogens, even in the absence of objective changes in the UCPP variables, may be beneficial in the management of common postmenopausal LUTS including frequency, nocturia, urgency, UUI, mixed urinary incontinence, and LUT infections [110–113].

An extensive literature review from 1998 on reproductive and hormonal risk factors for urinary incontinence first noted that systemic oral $E_2$ therapy was consistently associated with an increased risk of incontinence in older women [114]. One prospective, comparative study (the NHS study in 2004), and two large randomized, double-blinded placebo-controlled

population-based trials, (the HERS study 2005 and the WHI study 2005), have looked at the effects of systemic oral estrogen replacement therapy with and without progestins on the incidence and prevalence of urinary incontinence after the menopause. Their results show that conjugated equine estrogens, alone and combined with progestin, increased the risk of UI among continent postmenopausal women and worsened the characteristics of UI among symptomatic women [115–117].

The distribution of estrogen and progesterone receptor expression in the female LUT may offer a plausible explanation for the apparently different activity of female hormones on the LUT. Blakeman et al. found that estrogen receptors are almost exclusively situated in the squamous epithelium in the LUT, including in transitional cell epithelium in the proximal urethra and trigone that has undergone squamous metaplastic change. Except for the vaginal wall, no significant amount of $E_2$ receptors was found in the tissues deep to the epithelium [101]. These findings may explain why the main effect of topical $E_2$ in the LUT is on the inner urethral wall, producing a more efficient hermetic seal of the urethral lumen, whilst having little effect on the urethral supporting tissues. P. receptors can be localized in all tissues of the LUT. Their expression largely depends on the level of circulating estrogens, being significantly higher in premenopausal women than in postmenopausal women on hormone replacement therapy.

## Conclusion

Urethral function tests together with clinical epidemiological studies have contributed considerably to our knowledge and understanding of alterations in urethral function throughout a woman's lifetime. A constitutional or genetic predisposition and aging are the most prominent factors in the etiology of SUI and POP. Pregnancy is associated with a small but significant decrease in mean values of MUCPs, as can be observed in early pregnancy and urethral pressure variables do not change significantly during the course of pregnancy. Vaginal childbirth, especially the first, dilates and may damage supportive tissue of the pelvic floor, leading to a significant further decrease in MUCP and FUL when compared with early pregnancy values. Increasing age is associated with linearly decreasing MUCP and with a decline in collagen content in pelvic floor connective tissue of approximately 1 to 2% per year after the menopause. Consequently, women with constitutionally low intra-urethral pressure and weak pelvic floor supportive tissue, will be more liable to develop SUI and other urogenital disorders in later life. The age-related increase in pelvic floor disorders is most probably caused by an altered metabolism of so-called senescent cells. Senescent cells are cells that have entered a nondividing but viable phase: cell-cycle arrest. Senescent cells accumulate in organs during aging, are metabolically active, and participate in aging-related diseases, mainly by their secretory activity, commonly known as senescence-associated secretory phenotype [118]. Pregnancy, hormonal alterations, menopausal transition, and weight gain are at best of secondary influence in the pathophysiology of LUT dysfunction. How the decline in circulating estrogens induces the transition of fibroblasts into senescent cells at the level of the urogenital tract has not yet been elucidated.

**Authors' contribution** Hans van Geelen: data collection, data analysis, manuscript writing; Peter K. Sand: project development, editing.

## Declarations

**Conflicts of interest** None.

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