ABSTRACT. Co-morbidity between urological disorders, overactive bladder and urge incontinence first, and female sexual dysfunctions (FSD) is still underdiagnosed in clinical practice, in spite of data indicating an extremely high association between the two conditions. Latent class analysis of sexual dysfunctions by risk factors in women indicate that lower urinary tract symptoms have a RR= 4.02 (2.75-5.89) of being associated with arousal disorders and a RR=7.61 (4.06-14.26) of being associated with sexual pain disorders. Clinical history focusing on prepubertal signs and symptoms of overactive bladder (enuresis, nocturia, daily symptoms) indicate that 2.3% of women currently suffering of urge incontinence do report these early symptoms when actively asked for. Pathophysiological factors underlying co-morbidity between urge incontinence and FSD may begin in early infancy or adolescence. Estrogens may attenuate bladder' vulnerability at puberty. Their loss at menopause may re-trigger bladder overactivity, which remains borderline across the fertile age. Higher clinical and research attention is needed to further substantiate this preliminary finding and improve life-span designed preventive and therapeutic measures.

INTRODUCTION

The overactive bladder (OA) is a frequent and underreported condition affecting 11.4 to 17% of women over 40 years, with increasing incidence paralleling increasing age (1). It is characterised by uncontrolled contractions during the bladder-filling phase. Symptoms include an increased frequency of micturition, a strong and sudden desire to void and, if involuntary contraction is not suppressed, urge incontinence (UI).
Co-morbidity between urological disorders, OA and UI first, and female sexual dysfunctions (FSD), is still underdiagnosed in clinical practice, in spite of data indicating an extremely high association between the two conditions. Latent class analysis of sexual dysfunctions by risk factors in women indicate that lower urinary tract symptoms have a RR= 4.02 (2.75-5.89) of being associated with arousal disorders and a RR=7.61 (4.06-14.26) of being associated with sexual pain disorders (2).

Clinical history focusing on prepubertal signs and symptoms of OA (enuresis, nocturia, daily symptoms) well indicate that women currently suffering of urge incontinence do report these early symptoms when actively asked for (3). Pathophysiological factors underlying this co-morbidity may well begin in early infancy or adolescence (4, 5).

Unfortunately, a persisting communication failure still separates the pediatric world from the gynecological/urological one, puberty being a sort of invisible wall that separates the two clinical domains. The aim of this paper is to suggest a life span approach to urge incontinence. This could improve our understanding of different modulating factors (estrogens first) across the life span and encourage a more investigative approach to early pathophysiological factors that may increase co-morbidity between OA/UI and female sexual dysfunctions in adults.

THE EARLY PATHOPHYSIOLOGIC SCENARIO IN OA

2.3% of incontinent adults report to have had urge incontinence and/or nocturnal enuresis in their infancy (3, 6). Unfortunately prospective data on the percentage of girls who continue to display urge incontinence in adult life are scanty (6). In particular, in these patients, information about the so-called “toilet training period” is not available, underestimating the complexity of steps required to achieve the continence skill.

Between 1 and 3 years, the maturation of the cortical inhibitory pathways to the pontine micturition centre parallels the child’s ability to increase his/her continence competence. A progress that is mirrored in progressively fewer episodes of leakage. In parallel with the bladder expanding its size and filling capacity, the ability to completely suppress voiding at socially inappropriate times is progressively acquired. The child’s perception of this overactivity and his/her understanding of how to suppress it is determined by different factors. They depend on gender (3), individual ability and motivation to control (6), socially determined attitudes about continence (3-7), impulse control (9) and appropriate age to reach it (3-9). Genetically determined factors are increasingly recognized as contributors (10-12). When the cortical pathways between the parietal lobe and brainstem mature, the child finally learns to initiate voiding when the bladder is not full.

If during this “toilet training” critical period coercive methods are used, an overactivity of the external urethral sphincter may result. When a girl experiences urgency during childhood, she may increase the compensatory pursuit of a better continence through the contraction of the levator ani, as an adjunct strong sphincter controller. When active for years in childhood and adolescence, this coping muscular behaviour may contribute to a hypertonic pelvic floor, predisposing the young girl to vaginismus, dyspareunia and constipation (4, 5) with unexpected consequences on the urinary and genital area, considering the contiguity between them. The hypertonic muscle may then become a further contributor of the vicious circle that increases the detrusorial hyperactivity.

In a recent survey on 38 adolescent girls with persistent nocturnal enuresis and diurnal urge incontinence (8), 21% reported lifelong dyspareunia (coital pain) during intercourse, likely due to vaginismus. This disorder indicates the recurrent or persistent invol-
Urinary spasm of the musculature of the outer third of the vagina, which interferes with vaginal penetration, and which causes personal distress (13). In over 16% of these patients there is a gap between parental sphincter control requests and voiding competence achievement. Constipation was reported in 37%, well addressing the medical comorbidity underlined by pelvic floor dysfunctions. Patients who report a positive clinical history for early pressure to bladder control and/or had former enuresis are at increased risk of developing a transient urgency and frequent urination. Most of them, and women with UI, express a fear of losing urine during intercourse, a concern that may become a humiliating experience when leakage is during the orgasm, in adulthood. Recurrent vaginal and vulvar infection and inflammations may complicate the co-morbidity of a persisting OA and UI in infancy (4). Recurrence of vestibulitis and vulvovaginitis in girls and adolescents with urge incontinence may be related to an incorrect position of the legs adopted during micturition that gives rise to “vaginal micturition”, that would be more appropriate to call “vestibular micturition” (5). Urine may therefore irritate and cause chemical inflammation of the mucosa on the external side of the hymenal opening. The frequent observation in the same girls of a partial fusion of the labia minora (7) may explain the persistency of urine loss during urgency in the vestibular vaginal area and its irritating effect on the delicate vestibular tissue. Mast cell hyperactivation may follow, triggering the up-regulation of local immunitary-inflammatory response (14). Upregulation of the mast cell production of Nerve Growth Factor may precipitate and maintain the shift from nociceptive to neuropathic pain (see Graziottin, and Vincenti and Graziottin, this issue). This complex upregulation of local immunitary and pain-related responses may be a cofactor in the early onset of vestibular pain, even before the first intercourse, predisposing to vulvar vestibulitis syndrome and associated lifelong dyspareunia (5, 14).

When urge incontinence is associated with nocturnal polyuria, two different symptoms, probably accounted for by different sleep architecture and/or different threshold sensitivity to bladder signals, may be complained of (3, 4, 6-8, 15, 16):

- nocturnal enuresis (NE), when the girl and the woman cannot wake up,
- nicturia when appropriate night awakenings maintain the bladder competence.

A new emphasis on the pathophysiology of nocturnal enuresis has become essential for treating girls with this problem for two reasons, medical and psychosexual (4, 8, 15, 16).

The first one is that NE is not a self-limiting condition as traditionally expected, the prevalence in adult women varying from 0.5 to 2.3%. The second one is that the persistence of childhood enuresis is associated with a maturation delay of basic psychosexual needs: attachment, autonomy, sex identity, self-esteem and self-confidence (17, 18) which may impair adult sexual competence in a complex way. Indeed, feelings of inadequacy and incompetence, depression, loneliness, sadness, shame, anger and aggressiveness, guilty feelings and disappointment with parents, poor perception of locus of control, self limitations like living overnight outside home with friends or schoolmates, the search for perfection as frequent compensatory coping mechanisms, more in girls, are frequently reported (4, 6, 9, 17).

At puberty, the estrogen rise may indeed increase the bladder threshold to increasing filling volumes, acting both as a control enhancer and threshold stabilizer, through central and peripheral mechanisms. It therefore may seem that puberty “cures” the disorder, whilst it is just reducing one of key contributing factors, which remains borderline. This protective “estrogenic window” may show some clinical failures, with reappearance of
higher frequency and urgency, coherent with the underlying hormonal changes, during persisting amenorrhea in adolescent and/or during the amenorrhea in perurperium. After menopause, the exhaustion of ovarian production of estrogens, deprives women – who suffered from early OA and/or UI – of the estrogen-dependent protective help. Indeed, and in positive, a recently published multicentric, randomized, double-blind, placebo controlled study (level I of evidence) well indicate that 25 micrograms of estradiol applied topically to the vagina twice a week may significantly improve urogenital and sexual co-morbidity (19) (Table 1). They significantly improve bladder capacity, bladder volume at first stimulus and bladder volume at strong need to void, a finding of special relevance as it is documented by cystometry at baseline and after 12 months (Table 2) (19).

The parallel improvement of OA, UI, and the cohort of symptoms – nicturia first – and FSD with vaginal estrogen treatment after the menopause (19) again stresses the importance of a closer attention to the complex pathophysiology of this disorder and the powerful impact different levels of sexual hormones may have on its severity across the life span.

### CLINICAL APPROACH

Investigating childhood habits may help to identify a continuity between urge incontinence in girls and women. A well focused case history is mandatory in all women with this disorder. During the interview the doctor should be aware that a number of psychological factor may prevent reporting on this embarrassing topic. Indeed only 1/3 of affected women discuss their problem with a doctor or a nurse. Of these, 2/3 had suffered from OA and/or UI symptoms for two years.

Fear of rejection, shame, embarrassment, loss of self-esteem, all contribute to the difficulty a woman has in consulting her physician and asking for help (17, 18).

Active investigation on the part of the clinician is key in easing communication and avoiding the “closure of silence” that conceals both bladder and sexual problems in a common denial. Specific questions for a correct assessment are also suggested in order to identify whether the urge incontinence appeared in adult life or was also present in childhood. In case urge incontinence is associated with enuresis or nicturia some more fo-

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**Table 1 - Therapy of postmenopausal urogenital atrophy.**
Efficacy of treatment with 25 micrograms of 17-beta-estradiol applied vaginally twice a week, after 12 months, in a multicentric, randomized, double-blind, placebo controlled study (N=828 treated vs N=784 controls). From (19).

<table>
<thead>
<tr>
<th>Lower urinary tract symptoms and signs</th>
<th>p at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Urinary frequency and nocturia</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystitis</td>
<td>&lt;0.034</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Urinary atrophy</td>
<td>&lt;0.001</td>
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</tbody>
</table>

**Table 2 - Improvement of bladder capacity and urgency.**
Efficacy of treatment with 25 micrograms of 17-beta-estradiol applied vaginally twice a week, on bladder capacity and overactive bladder’ symptoms. Multicentric, randomized, double-blind, placebo controlled study (N=828 treated vs N=784 controls). Cystometric evaluation was performed at baseline and after 12 months of treatment. From (19).

<table>
<thead>
<tr>
<th>Maximal cystometric capacity</th>
<th>from 200 ml to 290 ml, p=0.023</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder volume at first urgency</td>
<td>from 140 ml to 180 ml, p=0.048</td>
</tr>
<tr>
<td>Bladder volume at strong need to void</td>
<td>from 130 ml to 170 ml, p=0.045</td>
</tr>
</tbody>
</table>
cused questions are asked to complete the picture.

Emotional and sexual intimacy has also to be investigated, as sexual identity, sexual function and sexual relationship may all be crippled by urge incontinence. Up to two thirds of affected women report they are less confident in courting and less willing to start a new relationship. One third prefers not to have orgasm for fear of leakage. More than half report their feeling of being less feminine and less sexually attractive: the smell of urine instead of the “scent of a woman” is difficult to accept for both men and women. Focusing on sexual function, an increasing number of women report a progressive loss of sex drive, more likely when this disorder is complicated by hormonal loss in the menopause. The quality of an intimate relationship may be impaired both in and outside the bedroom and may become a real challenge, particularly for newly formed couples. Even body image may change because of the depressing perception of a “bladder dominated” life.

Last but not least, urge incontinence may affect all dimensions of women’s life and self-esteem basis: few jobs can be sustained when a woman has to leave her place frequently and rush to the toilet to avoid the major humiliating disaster of an urge incontinence episode. Sexual identity, sexual function and sexual relationship may all change for the worse because of troublesome bladder symptoms: a concept that deserves the highest medical attention.

CONCLUSIONS

A life span perspective towards overactive bladder and urge incontinence may prove rich of new inspiration for a better understanding of underlying pathophysiology, to design more effective preventive and therapeutic measures. Increased awareness of complex co-morbidity between urogenital and sexual symptoms and their modulation by sexual hormones should further encourage physicians to break the “collusion of silence” by actively investigating both OA related symptoms and FSD in every consulting woman. A parallel evaluation of signs and symptoms of uro vaginal dystrophy should encourage a pragmatic therapeutic approach to relieve the hormone-dependent component of OA and UI. A detailed interview on the style and timing of toilet training, on the presence of recurrent lower urinary tract infection during childhood, constipation, and/or persistence of nocturnal enuresis over 6 years is mandatory in all adult women with urge incontinence. Indeed, unaddressing dysfunctional voiding habits in childhood and adolescence and associated medical and psychosexual comorbidity may have a wide range of late consequences, impacting on sexuality, quality of emotional intimacy, and overall quality of life.

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