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Pathogenesis of OAB and surgical treatment according to the Integral Theory Paradigm

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A B S T R A C T

Overactive bladder (OAB is a definition by the International Continence Society (ICS). It comprises three symptoms, urge, frequency and nocturia. It is a major problem for elderly women. OAB is generally assumed to be a paradigm, but it cannot meet the criteria of a paradigm, as its causation is said to be "idiopathic" (unknown). In 1993, it was demonstrated that the sequence of events in urodynamically diagnosed detrusor overactivity was identical with what occurred in normal micturition, which lead to the conclusion that frequency, urgency, nocturia were in effect, an uncontrolled micturition. Data from a 1997 experiment indicated the control mechanism of the bladder was binary, either closed or open, regulated by a peripheral musculoligamentous system under cortical control. The Integral Theory paradigm's view of OAB was evolved which is based on and compatible with ICS definitions and descriptions. The OAB condition is an uncontrolled prematurely activated micturition; pathogenesis: anatomical defects along control mechanism pathway, but mainly damage in the peripheral musculoligamentous system; specific tests to prove causation: mechanically supporting suspensory ligaments, "simulated operations"; treatment of the cause: squatting-based exercises to strengthen the muscles, ligament repair by plication or slings.

1. Introduction

According to Thomas Kuhn, perhaps the leading 20th Century philosopher of science, the development of science is driven by what Kuhn called a 'paradigm'.[1] In medicine, any paradigm for a particular condition, involves stating the condition, its pathogenesis, specific tests to prove causation and treating the cause. What is generally considered by physicians as the "OAB (overactive bladder) paradigm" will be examined in this light: the condition is bladder urgency, frequency, nocturia. Pathogenesis is unknown. Specific tests to prove causation: urodynamics measure pressure or flow, but do not indicate causation. Treating the cause: there is no known cause. Treatment is symptomatic and empirical. It can be concluded that there is no such thing as an OAB paradigm.

The concept of OAB for treatment of bladder incontinence has been driven over the years by successive definitions of the International Continence Society (ICS), beginning with the First ICS report in 1976.[2] In the ICS first report on the standardisation of terminology of lower urinary tract function in 1976, there was no such concept as "OAB." There were only symptoms of frequency, urge, nocturia. Urgency was "a compelling need to urinate which is difficult to defer (pain, pressure, discomfort)"; nocturia was "waking to pass urine during the main sleep period"; increased urinary frequency was "a complaint that voiding occurs more frequently than deemed normal by the individual (or caregivers)".

The first ICS report in 1976, drew a sharp division between stress urinary incontinence (SUI) and urge incontinence (UI), drug treatment for the latter surgery for the former, but only if there was no "detrusor instability" (DI, now DO "detrusor overactivity"), which needed to be excluded by urodynamics, because of the likelihood of failure. It needs to be noted, however, that in 1976, the standard operation for SUI was the Burch operation, which had a high rate of de novo urgency. This was probably due to the pressure put on the urothelial stretch receptors "N" ,Fig. 1A), from below, by forcibly elevating the vagina to attach it to Cooper's ligament.

Urodynamically diagnosed "DI", now "DO", was considered then and it remains, now, according to the ICS, the definitive test for an unstable bladder, even though repeated publications show that less than 50% of patients with urge symptoms have urodynamic "detrusor

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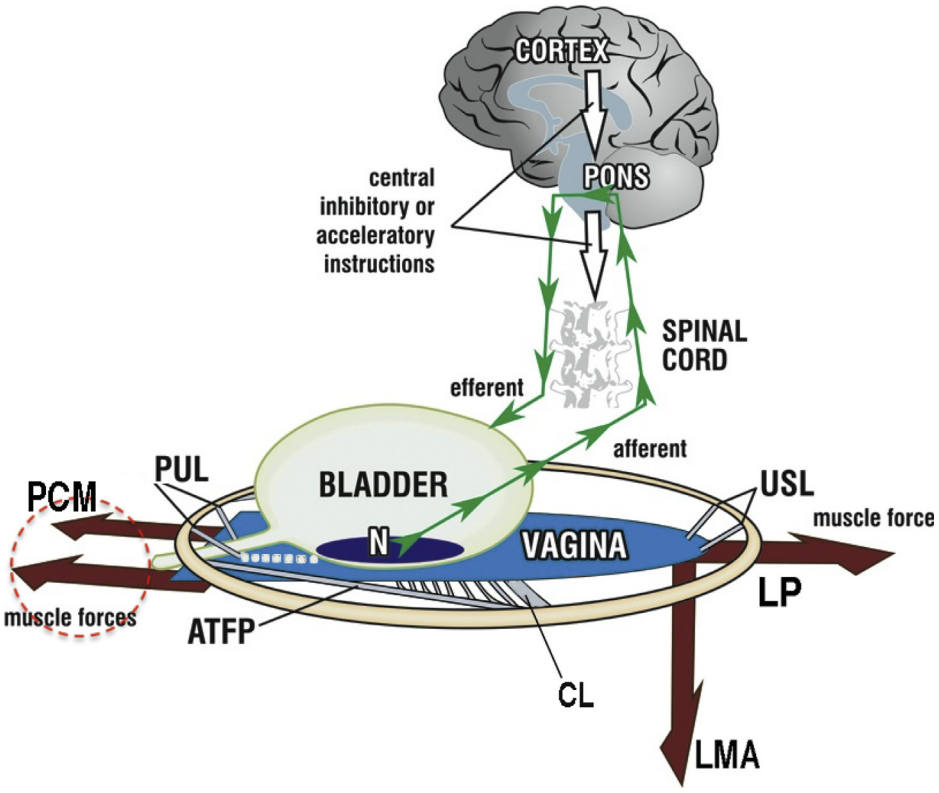

Fig. 1A. Control of bladder is binary Schematic 3D sagittal view. System in normal closed mode. Cortical control: afferent impulses from stretch receptors 'N are reflex suppressed cortically (white arrows). When required, the cortex activates the micturition reflex.

overactivity'(DO)"[3,4] and even though the pressures and flow characteristics recorded only confirm what is already clinically known, not causation.

In fact, little has changed since 1976. Medical treatment was based on the theory that urge incontinence was due to some kind of neurological defect, either within the brain or spinal cord, or an intrinsic cause within the bladder wall itself. As such, urge incontinence is not amenable to surgical treatment, requiring medical treatment to suppress the uninhibited detrusor contractions. Surgery has always been deemed as a contraindication for treatment of OAB by the ICS and other learned bodies, even today, except as an end stage procedure such as an ileal bladder.

The concept of "OAB" (overactive bladder) originated as a definition from the 2003 ICS report.[5] Though the name "OAB" implies that the cause is actually in the detrusor itself (one of Peyronnet's "phenotypes"), the ICS has never stated such. Most treatments, for example anticholinergics, botulinum toxin, are empirical and seek to prevent the detrusor contracting. Such treatments have their own complications, for

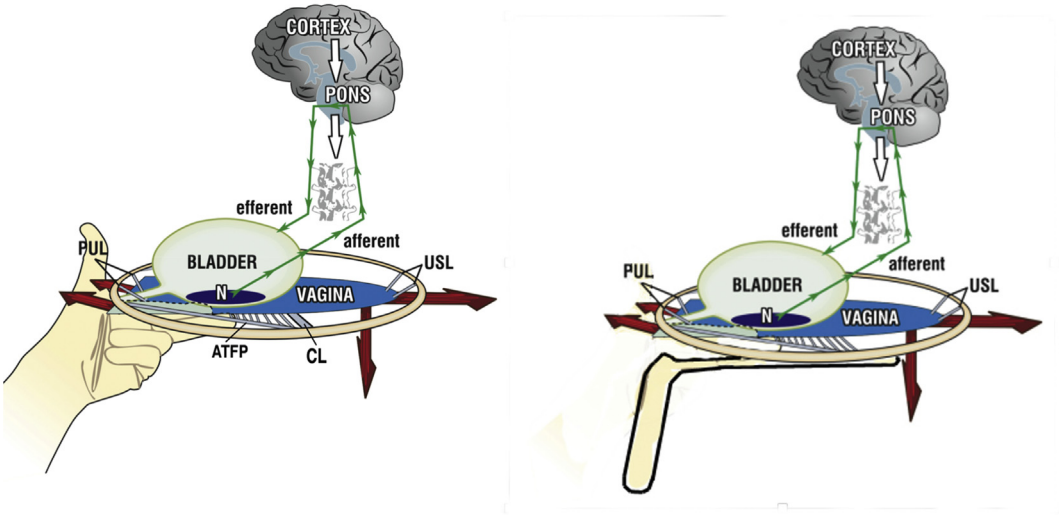

Fig. 1B. Diminution of urge by "simulated operations". Simulated operations work by mechanically supporting ligaments in the way a sling would. The speculum is very gently inserted into the apex of the vagina. This stretches the vagina and supports the uterosacral ligaments (USL). The mechanical support restores firmness to the USL insertion point, so the vagina can now be stretched to support "N" and diminish the afferents to the brain. Digitally supporting the bladder base (left figure) will also relieve urge symptoms if gently performed. Excess pressure with worsen urge sensation. Both demonstrate the existence of bladder base stretch receptors.

anticholinergics, dry mouth, constipation, even Alzheimer's Disease[6]; one bothersome and not infrequent complication of botulinum toxin is urinary retention and urinary tract infections.[7] More recent treatments include sacral nerve stimulation, a very expensive and only partly effective treatment (50% improvement in some studies is considered a "cure"), one which requires patients to have implanted wires in their spine for the rest of their lives. The basis of this treatment is essentially unknown.

More than 35 years after the First Report,[2] experts from the International Consultation for Incontinence (ICI) stated that the cause of "OAB" was still as yet unknown and treatment was still unsatisfactory[8] In 2019, Peyronnet et al.[9] confirmed this statement. Seeking a way forward, they presented several hypotheses "future phenotypes", as possible causes and possible research directions for future treatments of OAB.

1.1. OAB summary 2021

According to the ICI,[5] the pathogenesis of OAB is unknown, investigation by urodynamics has only a 50% diagnostic rate, and there is no known cure. The very name OAB is inappropriate, as it implies that the cause is within the detrusor itself.

It is worth to emphasize again that the ICS has never stated the OAB originates from the bladder wall. The popular concept of OAB originating from the bladder wall is easily invalidated. Inserting the lower blade of a bivalve speculum[10] (Fig. 1B), stretches the vagina to support USLs and immediately relieves urgency and chronic pelvic pain in about 70–80% of women with these symptoms.

With reference to Fig. 1A, the vagina is suspended by ligaments from the pelvic brim, uterosacral ligaments (USL), pubourethral (PUL), cardinal (CL) ATFP. "N" represents stretch receptors which are supported by the underlying vagina which is tensioned by oppositely acting reflex muscle forces (large arrows). The small green arrows represent afferent impulses to the brain (right side) and also, efferent (left side).

These two simple manoevres (Fig. 1B), immediately invalidate any possible pathogenesis within the detrusor muscle, including all of Peyronnet et al.'s "phenotypes" except "urothelium/suburothelium and bladder afferent nerves" which, in fact, are a central part of the Integral Theory Paradigm. They were predicted in the 1990 Integral Theory and were urodynamically confirmed in 1999.[11,12]

At first sight, viewed within the context of Thomas Kuhn's views of paradigms,[1] OAB has all the features of a failed paradigm. Despite the ever increasing evidence by those following the Integral Theory paradigm that at urge incontinence "urge", "frequency", "nocturia" are surgically curable,[13–26] learned bodies such as ICI ignore peer review data published in PubMed journals and continue to teach that OAB is not surgically curable. All the elements of OAB as defined by the ICS, urge, frequency, nocturia are testable as per Fig. 1B and cured or improved by surgically repairing laxity in two main ligaments, native ligament repair[28] (Figs. 7 and 8), with uterosacral tapes[13–26] or strengthening with squatting-based pelvic floor exercises.[27]

1.2. OAB as "uncontrolled micturition"

The proofs of the Integral Theory's paradigm that urge, frequency, nocturia (OAB) are an uncontrolled micturition[11] governed by a feedback process (Fig. 1A),[12] were in fact based on ICS definitions and descriptions and do not conflict with ICS definitions, current or otherwise. With reference to Fig. 1A, the Integral Theory paradigm states that any anatomical defect may cause OAB: cortical, spinal, peripheral nerves, inflammation, cancer or inflammation at bladder base ("N"), damaged ligaments, damaged muscles. However, a 35-year experience by the author indicates that "idiopathic" OAB, no known cause, at least in females, is mainly caused by loose ligaments weakening the muscle forces which close and open the urethra (Fig. 1A).

With reference to Fig. 1A Peripheral control is by a musculo-elastic mechanism which responds to cortical efferent (small arrows).

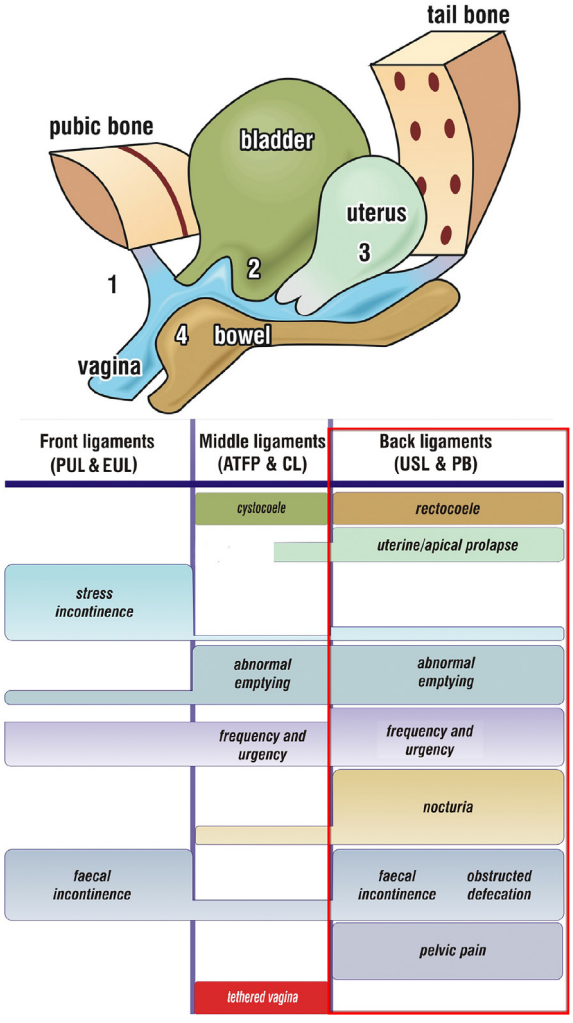

Fig. 2. Pictorial diagnostic algorithm. The pictorial diagnostic algorithm relates symptoms to ligament damage. It is diagnostic and serves as a guide to surgery. The connective tissue structures causing prolapse and pelvic symptoms fall naturally into 3 zones, front, middle and back. The main ligaments causing the symptoms and prolapse in each zone are indicated in capital letters, two in each zone: PUL pubourethral ligament and EUL external urethral ligament are Anterior ligaments; ATFP arcus tendineus fascia pelvis and CL cardinal ligament complex are Middle ligaments; USL uterosacral ligament and PB perineal body are Posterior ligaments. Chronic pelvic pain and nocturia are uniquely caused by uterosacral (USL) ligament laxity and SUI by pubourethral (PUL) damage.

The three directional muscles (large arrows), forward, pubococcygeus muscle "PCM ", backward, levator plate" LP", and downward, conjoint longitudinal muscle of the anus "LMA" contract against the supporting ligaments, PUL (pubourethral) and USL (uterosacral), to stretch vagina tightly much like the membrane of a drum. The stretched vagina supports the urine column, preventing activation of the stretch receptors "N", decreasing afferent impulses to the cortex.

Micturition. Central control (white arrows) relaxes and PCM (broken circle) relaxes allow the posterior muscles LP and LMA to unrestrictedly open out the posterior wall of urethra (white broken lines) just prior to bladder evacuation by global detrusor muscle contraction. CX = cervix; CL = cardinal ligament; ATFP = arcus tendineus fascia pelvis.

Dysfunction. Weakness in the muscles PCM, LP, LMA and/or the ligaments they contract against, PUL, USL, will affect the ability of the peripheral control mechanism to mechanically close urethra (incontinence), open it (obstructed micturition) or control micturition by bilateral stretching of vagina by the 3 opposite muscle forces to support "N"(urge incontinence).

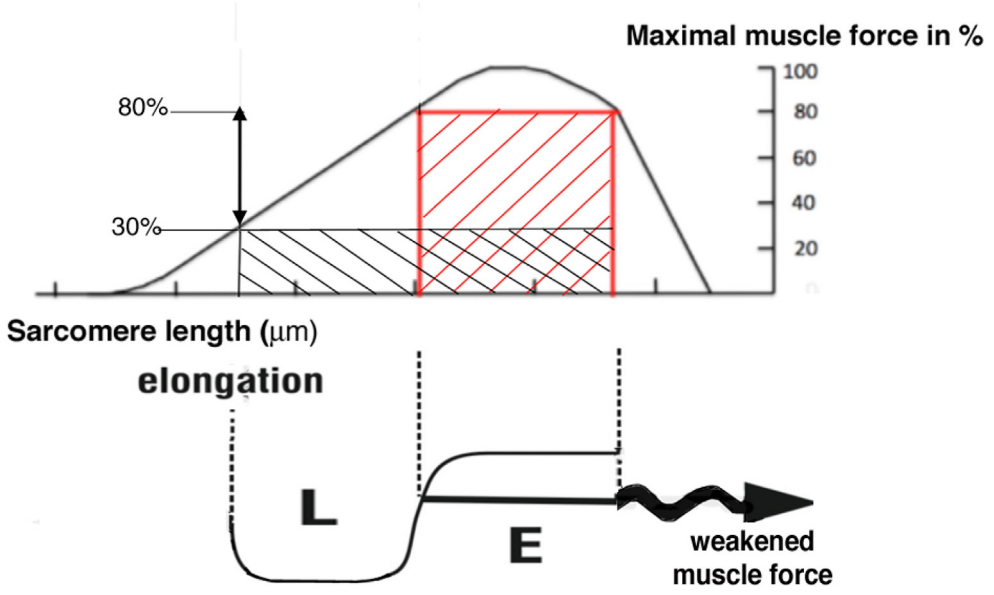

Fig. 3. Gordon's Law. A striated muscle contracts optimally over a short length only, 'E', red square. If the insertion point is loose, the muscle effectively loosens 'L'. Lengthening the muscle 'L', results in a rapid loss of contractile force, black rectangle.

Left Fig. 1B. Gentle digital support of bladder base supports the hydrostatic pressure of the urine and prevents it activating the stretch receptors "N" at bladder base. The number of afferents to the cortex are therefore diminished and the feeling of urge subsides.

Right Fig. 1B. Inserting the lower half of a bivalve speculum will relieve urge by restoring the contractile strength of the posterior pelvic muscles; it relieves chronic pelvic pain by supporting the USLs which support the Frankenhauser and sacral plexuses.

1.3. Integral Theory Paradigm (ITP) and surgical cure of OAB

The ITP uses symptoms to diagnose which damaged ligaments are causing pelvic floor symptoms and even pelvic organ prolapse (Fig. 2). The Integral Theory paradigm states that urge incontinence is the cortical sensation of a prematurely activated, but otherwise normal micturition reflex.

Grouped symptoms (Fig. 2), are an obligatory condition for diagnosing ligamentous causes of OAB, *and these may occur with very minimal prolapse.* According to the ITP, urge incontinence is NOT a standalone symptom. Urge incontinence in women is mainly a component of the Posterior Fornix Syndrome (PFS), (posterior zone, Fig. 2). PFS was first described by Petros & Ulmsten in 1993, as part of the 2nd iteration of the Integral Theory.[28] The original PFS symptoms were urge, frequency, nocturia, chronic pelvic pain, abnormal emptying and/or urinary retention.[29] PFS has expanded to include anorectal symptoms associated with USL laxity, fecal incontinence and obstructive defecation, posterior zone (Fig. 2). Surgical cure of all posterior zone symptoms has been prospectively validated many times, by many surgeons, with large data.[13–26]

How to use the pictorial diagnostic algorithm. Because symptoms such as urgency and abnormal emptying may be caused by ligament damage in more than one zone, all rectangles for that symptom should be ticked. The area of the symptom rectangles indicates the estimated frequency of symptom causation occurring in each zone. The numbers in the figure correlate with structural damage and with ligament damage; 1: USI; 2: cystocele; 3: uterine prolapse; 4: rectocele. *It is emphasized that major symptoms may occur with minimal ligament damage.*

The pathogenesis of PFS symptoms is summarized in Figs. 1 and 2. A key prediction of the Integral Theory, the presence of stretch/pressure receptors "N" (Fig. 1A), remained controversial until the early 2000s.

In 2008, Everaerts et al.[30] wrote a description of urothelial stretch receptors with transient receptor potential (TRP) channels in the bladder wall linked to afferent A-delta fibres. These fibres were the afferent limb of the micturition reflex (Fig. 1A). Also present were unmyelinated C-fibres. Discovery of urothelial stretch receptors and unmyelinated pain fibres confirmed important predictions of the 1990 Integral Theory,[31] that stretch and pain receptors, "N" (Fig. 1A), at bladder base, sent afferent signals to the cortex which beyond a critical mass, activated the micturition reflex which was perceived by the cortex as urgency, at night, nocturia; this perception, in turn, was caused by an inability of the three oppositely acting pelvic muscles forces (large arrows, Fig. 1A) to stretch the vagina sufficiently to support the stretch receptors "N" from below (Fig. 1A); this failure to adequately support the stretch receptors was caused by lax cardinal/uterosacral ligaments against which the muscles contract (Fig. 1A).[31]

The peripheral control mechanism (Fig. 1A), functions very much like a trampoline, with the vagina the trampoline membrane and the ligaments acting as trampoline springs. Striated muscles require a firm insertion point to contract maximally.[32] If PUL or USL are loose (Fig. 1), the striated muscles contracting against them effectively lengthen (Fig. 3) and their contractile force weakens.[32]

Inability of either the front or back reflex muscle forces to tension the bladder base sufficiently to support the stretch/pain receptors "N" (Fig. 1A), allows excess afferents from "N" to reach the cortex and activate the micturition reflex. This is perceived as urge symptoms. If the micturition reflex, though activated cannot be suppressed, the patient wets. Stimulation of the unmyelinated C fibres may be the cause of bladder pain. However, the chronic pelvic pain often seen in such patients may have a different origin, inability of loose USLs to support the T11-L2 and S2-4 visceral nerve plexuses, Fig. 4.[33]

Chronic pelvic pain (Fig. 4), often co-occurs with OAB, emptying problems, nocturia as part of the posterior fornix syndrome.[28] It has no or little relationship to the feedback control system of the bladder. All the PFS symptoms, for different reasons, have a common origin, loose USLs. The pain experienced by the patient is a referred pain and the site of the pain varies according to the distribution of the nerve plexus. For example, low abdominal pain, bladder pain, rectal pain could be attributed to T11-L2; vulvodynia, perineal pain, sacral pain, perianal pain, paraurethral pain to S2-4 plexus. All can be relieved by a speculum inserted

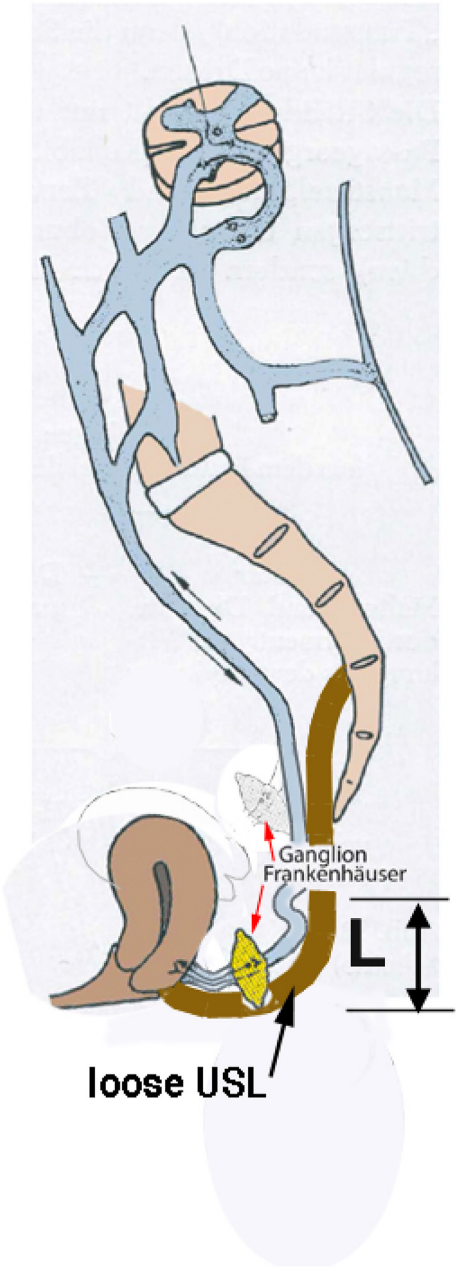

Fig. 4. Pathogenesis of chronic pelvic pain. The Ganglions of the Frankenhauser T11-L2 and the Sacral Plexuses S 2–4 are supported by uterosacral ligaments (USL) at their uterine end. 'L' indicates ligament laxity. The posterior directional forces are weakened and cannot stretch the USLs sufficiently for them to support the nerves. The nerves may be stimulated by gravity or by the prolapse or by intercourse to fire off and be perceived as pain by the cortex.

into the posterior fornix[10] (Fig. 1B).

Surgical cure of OAB by CL/USL repair – is it effective for symptoms?

Experience with younger women with chronic pelvic pain of unknown origin and presumably good USL collagen has shown good cure rates for chronic pelvic pain and urgency with native tissue USL plication at 12 months.[29] Shkarupa, Table 1, achieved excellent cure rates for prolapse, urge, frequency, nocturia at 18 months, but only in premenopausal women. Shkarupa proved the futility of native tissue repair for prolapseand symptoms in postmenopausal women. The results in post-menopausal women, Table 1, were catastrophic. He concluded post-menopausal women required a tape to create new collagen. This view was validated by Inoue et al.,[19] who achieved 5 year cure rates of

Table 1
Cure rate (%) of POP and overactive bladder symptoms at different points of follow-up (Published by permission, Shkarupa et al.[34]).

POP/OAB symptoms	Pre-menopausal group (n = 40)	Post-menopausal group (n = 48)
3 months		
Frequency	75	62.5
Urgency	87.5	77
Nocturia	95	68.8
POP	97.5	89.6
6 months		
Frequency	77.5	50
Urgency	85	68.8
Nocturia	97.5	62.5
POP	87	52
12 months		
Frequency	62.5	39.6
Urgency	82.5	31.3
Nocturia	75	29.2
POP	80	20.8
18 months		
Frequency	60	14.6
Urgency	67.5	16.7
Nocturia	87.5	18.8
POP	80	16.7

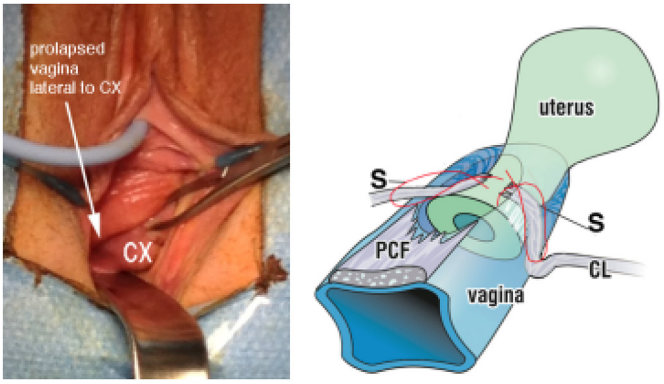

Fig. 5. Clinical diagnosis of cardinal ligament (CL) dislocated from the cervical ring. Left. Vagina typically prolapses down on the lateral side of the cervix when CL is torn.

79% for prolapse and high cure rates for urge, nocturia, frequency, chronic pelvic pain in a group of 70 year old women using tapes to repair damaged ligaments.[19]

1.4. Diagnosis of CL defect by vaginal examination

Right. The left CL, Fig. 5, is seen dislocated from the anterior cervical ring and prolapsed downwards. Pubocervical fascia (PCF), Fig. 5, is also torn from its attachment to CL and cervix; S = sutures re-attaching two sides of CL onto the cervix.

Native tissue surgical technique for cardinal ligament (CL) repair.

VIDEO: Native tissue CL repair, https://youtu.be/aJDPOELZZfc.

The aim is to shorten and therefore, strengthen the ligaments by plication.

All steps in the surgery are performed with the vagina stretched and under tension. The cervix is pulled towards the surgeon. A transverse incision is made 1 cm above cervix or hysterectomy scar at the junction of bladder to cervix. The bladder is dissected off the cervix or vagina in patients with previous hysterectomy, initially with scissors, then with finger dissection. The purpose of this dissection is to ensure that the ureters are well away from the field of surgery. Ensure the bladder is grasped with forceps to provide counter tension. This will facilitate dissection, especially if there is scarring from previous surgery. The CL

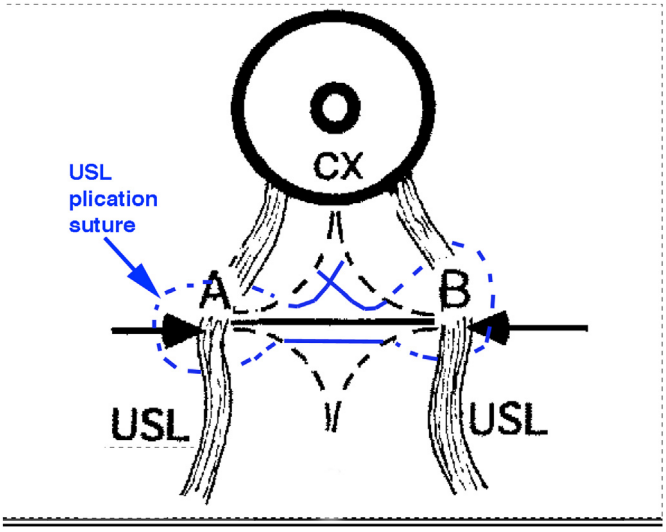

Fig. 6. Plication of uterosacral ligaments (USL). A 5 cm transverse incision is made at the apex of the enterocele bulge usually about 4–5 cm below the cervix (CX). The incision is opened out with a speculum. The enterocele is dissected off the USLs. A No1 vicryl suture is inserted laterally into the USLs and associated tissues and the USLs are approximated. When the patient is post-menopausal add a tape to create new collagen.

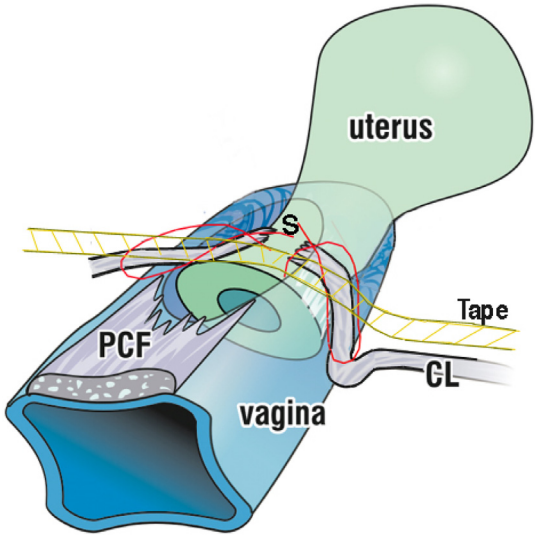

Fig. 7. Cardinal ligament repair with a tension-free tape for post-menopausal women. Native tissue CL repair is performed. A 10 cm tape is added to create new collagen to reinforce the ligaments.

ligaments are located at 9 and 3 o'clock. Tensioning the lateral ends of the vaginal incision is the best way to locate the CLs. Using a large needle with 0 proline, nylon or PDS, the ligaments are approximated to the midline with two sutures. If the ligaments cannot be accurately located, take two wide sutures inferolaterally, (this is where the displaced CL ligaments are located, and approximate. The tissues taken up are invariably attached to the ligaments and the sutures will automatically approximate them. Close the vaginal epithelium with 00 vicryl.

Native tissue surgical technique for uterosacral ligament (USL) repair.

VIDEO: Native tissue USL repair, https://www.youtube.com/watch?v=MGLdYHtqxzg.

1.5. The aim is to shorten and therefore, strengthen the ligaments by plication

A full thickness transverse incision 5cm wide is made about 4 cm below cervix or hysterectomy scar at the apex of the enterocele bulge. Under counter tension, the enterocele is gently dissected off the vagina, but is not entered. USL ligaments are located digitally by stretching the vagina, then grasped with strong forceps, then secured and approximated with a large (No1 needle) with 0 proline, vicryl or PDS, to the midline with two sutures. The suture is not cut, but retained for the next step, approximation of rectovaginal fascia to the USLs. The same needle approximating USLs is used to perform a purse-string ('tobacco pouch') suture 1 cm from the cut vaginal edge. This suture is inserted into the rectovaginal fascia (musculoelastic layer of vagina) and is then tied deep into the already approximated USLs. Close the vaginal epithelium with 00 vicryl.

For post-menopausal women, major deterioration of symptom cure was seen after 3 months, falling to as low as 20% at 18 months, Table 1. In contrast, long term cure at 60 months in a group of 70-year old women using a TFS CL/USL sling[19] has been reported for both pain and urge. We attribute the former to collagen leaching out of the repaired USLs and the latter to new collagen created by the tapes.

Is an expensive kit required? No. A tape placed "tension-free" after the native tissue plication as described will create new collagen to give a long-term result.

Adding a tension-free tape to native tissue ligament repair.

Shkarupa[34] has demonstrated that post-menopausal women have a much higher failure rate with native tissue ligament surgery. Applying a tape along the lines of the plicated ligaments creates new collagen to reinforce these damaged ligaments. The author has successfully performed several hundred of these operations.

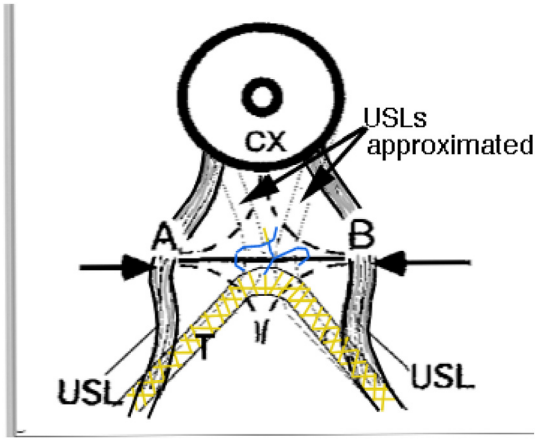

Fig. 8. Uterosacral ligament repair with a tension-free tape for post-menopausal women Native tissue USL repair is performed. A 10 cm tape (T) is added to create new collagen to reinforce the ligaments.

The ligaments are shortened by plication exactly as per native tissue repair (Fig. 5&6). A tape 10 cm long and 1 cm wide is fashioned from a hernia mesh. Each 5 cm arm is grasped with a suitable Crile or other forceps and literally slipped below the vaginal epithelium in the direction of the ligaments: laterally for CL(Fig. 7), posteriorly for USL(Fig. 8). Usually little or no dissection is required to slip the tape between the plicated ligament and the vagina. The vaginal incision is then sutured (see Fig. 6).

1.6. Cure by surgical reinforcement of CL/USL[13–26]

The accumulated data from such cures of urge, frequency, nocturia and chronic pelvic pain cannot be denied. One multicentre study of 1420 patients alone,[17] prospectively cured apical prolapse, chronic pelvic pain, urgency and nocturia in post-menopausal women, using two posterior slings which reinforced weak USLs.

2. Conclusions

A speculum ("simulated operation") gently inserted into the posterior fornix confirms USL aetiology by alleviating pain and urge symptoms. It also directly invalidates any theory of OAB originating in the detrusor muscle and many other "phenotypes"[9] such as metabolic syndrome, sex hormone deficiency, urinary microbiota, gastrointestinal functional disorders, and subclinical autonomic nervous system dysfunctions. The role of urothelium/suburothelium and bladder afferent nerves have been part of the Integral Theory paradigm since 1990.[31] Understanding of ligament pathogenesis and diagnosis, speculum/digital support of bladder tests to confirm algorithm diagnosis, cure by USL repair have been practised and reported by followers of the Theory since 1993.[13–26] Regarding OAB as an uncontrolled micturition caused by anatomical defects in the binary control model, opens up new nonsurgical and surgical avenues of cure. Which ligaments to repair are guided by the diagnostic algorithm, which uses symptoms to predict ligament damage.

Conflicts of interest

No conflict of interest.

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