Peer Review File

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Review Comments

Reviewer A

Dear colleague,
As editor of the ATM special series on Integral Theory paradigm, to which this article you reviewed belongs, I have been asked to reply to your very detailed critique, as your questions necessarily will require us to deliver to you the basic science of micturition, clinical, surgical, anatomical, urodynamical, and especially, biomechanics, and flow mechanics.

Firstly, however, I thank you sincerely for your comments. They eruditely present the traditional views on the anatomy of normal and abnormal micturition disorders, most of which we do not fundamentally disagree with. Our studies over 20 years take the mechanics a couple of steps beyond observational descriptions which is the essence of the ICS writings. We are familiar with much of the contents by authors of the Abrams book, much of it based on observations, which are quite different from pathogenic anatomical pathways, which is what the Integral Theory is all about.
Like you, we adhere to the tenets of the scientific method, which demands answers to the questions posed. Your questions are very detailed, as will, of necessity, be the answers.

My answers are in blue type
It is relevant to state this paper is part of an update series of 19 related papers on the Integral Theory paradigm (IT), all of which followed a set template: brief, approximately 1600 words, enhanced by videos and figures. We needed to expand well beyond these limitations in our replies.

PLEASE NOTE The IT, except for some aspects of "OAB", is compatible with the ICS definitions (See Petros P, Quaghebeur J, Wyndaele JJ. An anatomical pathogenesis of lower urinary tract definitions from the 2002 ICS report symptoms, conditions, syndromes, urodynamics. Neurourol Urodyn. 2022 Mar;41(3):740-755. doi: 10.1002/nau.24889. Epub 2022 Feb 16. Erratum in: Neurourol Urodyn. 2023 Jun;42(5):1169. PMID: 35170804; PMCID: PMC9306741.)

Reviewer A - Comment 1: This is a theoretical study on the relationship between uterosacral ligament (USL) injury and underactive bladder (UAB) and Fowler's syndrome (FS) in women.

Reply: Some parts are theoretical and these will be addressed in the appropriate segment, but let's start from the published data of UAB cure. **Challenging UAB and Fowler's Syndrome (FS) criteria by USL sling surgery**.

In urodynamically validated surgical studies, Goeschen *et al.* (12), Petros (11,13,) and Himmler *et al.* (14) followed posterior fornix syndrome (PFS) protocols for diagnosis and surgery to repair USL laxity, using posterior slings. The abnormal emptying ("UAB") symptoms cured were similar to those reported in the Fowler's Syndrome and UAB ("underachieve bladder") study (4).

4. Petros P, Abendstein B, Swash M. Retention of urine in women is alleviated by uterosacral ligament repair: implications for Fowler's syndrome. Cent European J Urol 2018;71(4):436-43. [PubMed]

10. Petros PE. New ambulatory surgical methods using an anatomical classification of urinary dysfunction improve stress, urge, and abnormal emptying. Int Urogynecol J 1997;8(5):270-8. [PubMed]

11. Goeschen K, Gold DM. Surgical cure of chronic pelvic pain, associated bladder and bowel symptoms by posterior sling in 198 patients validates the Pescatori Iceberg principle of pelvic symptom co-occurrence Pelviperineology 2017;36:84-8.

12. Petros PEP, Richardson PA. TFS posterior sling improves overactive bladder, pelvic pain and abnormal emptying, even with minor prolapse –a prospective urodynamic study. Pelviperineology 2010;29:5255.

14. Himmler M, Kohl M, Rakhimbayeva A. et al. Symptoms of voiding dysfunction and other coexisting pelvic floor dysfunctions: the impact of transvaginal, mesh-augmented sacrospinous ligament fixation. Int Urogynecol J 2021;32(10), 2777–86. [PubMed]

Reviewer A - Comment 2: The authors conclude that both conditions are effect of USL injury and that therefore, the repair of this structure can cure both conditions.
Reply: See surgical data above, improvement of UAB by USL repair.

Reviewer A - Comment 3: However, these conclusions are not enough supported by the authors' reasoning for several reasons.
The most important reason is that this is a theoretical and therefore deductive reasoning that needs the premises to be true, because from false premises we cannot draw any valid conclusion.
The premises presented by the authors are the following:

1st. "For micturition to occur, the forward vector "PCM" relaxes, so the backward/downward levator plate/ conjoint longitudinal muscle of the anus muscle temporarily dominate and pull open the posterior wall of the urethra to facilitate micturition".
This premise is wrong. Bladder neck opening is a mechanical event because the

hydrostatic bladder pressure exceeds the hydrostatic urethral pressure.
During the pre-void phase there is a progressive increase of bladder pressure due to detrusor contraction and a decrease in urethral pressure due to inhibition of sympathetic stimulation of urethral smooth muscle and pudendal inhibition striated external sphincter.

Reply: It is a concern in science when someone makes a categorical statement" This premise is wrong." That is what was said when Ulmsten and I first published our data for the midurethral sling which is based on the Integral Theory (IT). What was stated in this paper on UAB, is also based on the Integral Theory of female Urinary Incontinence published with 79 pages of experimental proofs in ACTA Obstet et Gynecol Scandinavica in 1990. Answers to many of the reviewers questions can be found in the original 1990 Theory.

https://obgyn.onlinelibrary.wiley.com/toc/16000412/1990/69/S153

The foreword by Professor Axel Ingelman-Sundberg, co-founder of IUGA is relevant to your questions: control of the bladder is from outside of it.

> *To me it has always been obvious that in general the reason behind female urinary incontinence has to be looked for outside the bladder i.e. in the structures supporting the urethra and bladder neck - specifically ligaments, pelvic floor muscles and vagina. If symptoms of urinary incontinence arise from a dysfunctional anatomy in the aforementioned structures then function should come with restoration of anatomy. Axel Ingelman-Sundberg.*

Reviewer A - Comment 4: "and a decrease in urethral pressure due to inhibition of sympathetic stimulation of urethral smooth muscle"

Reply: The above comment has never been scientifically proven. We know for a 1993 urodynamic study that the muscles which close the distal urethra, PCM (pubococcygeus muscles) relax immediately prior to micturition, evident in figure3 below and the 1997 micturition xrays.

See Petros PE, Ulmsten U. Bladder instability in women: A premature activation of the micturition reflex. Neurourol Urodynam. 1993;12:235-239 .

Reviewer A - Comment 5: Bladder neck opening is a mechanical event because the hydrostatic bladder pressure exceeds the hydrostatic urethral pressure.

Reply: Obviously, as otherwise there could be no evacuation of urine. The IT adds another element" clearly seen in figure3: the posterior urethral wall is actively displaced downwards and backwards, obviously by external forces*. Radioopaque

dye had been injected into the rectum, vagina, and levator plate (LP). Vascular clips were inserted in the vagina, at midurethra, bladder neck, bladder base, and the xrays at rest and micturition were superimposed. The vagina (which is anatomically attached to bladder base by the vesico-vaginal ligament) is stretched open by downward angulation of the levator plate. See broken lines in figure2, where the urethra is pulled open from "C" closed to "O" open.

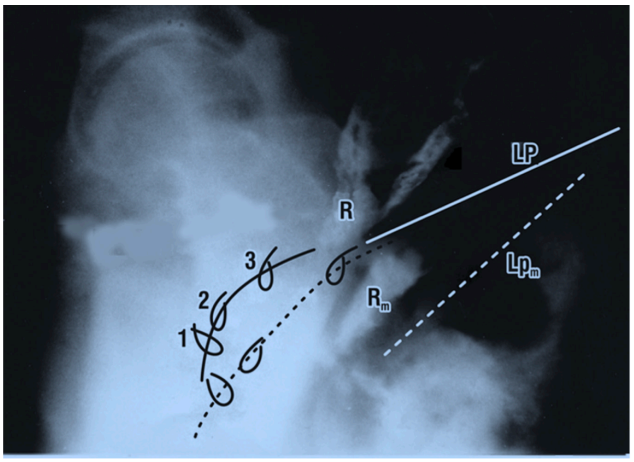

Figure 3 Xray of normal micturition (broken lines) superimposed on a resting vagina (unbroken lines). Superimposed xrays, rest and micturition. Unbroken lines at rest. Broken lines at micturition (m). Vascular clips have been applied to 1. midurethra, 2. bladder neck. 3. bladder base. The vagina is stretched backwards and downwards by downward angulation of levator plate LP_m at micturition. LP=position at rest; R=rectum at rest; R_m=rectum at micturition. Note backward/downward extension of all three vaginal clips during micturition, validating active muscle action apparently by downward angulation of LP.

Reviewer A - Comment 6: 2nd "because the hydrostatic bladder pressure exceeds the hydrostatic urethral pressure."

Reply: In a mathematical based on mechanical tissue characteristics and a detrusor pressure of 160cm, it was calculated that a hydrostatic pressure 2 orders of magnitude(x100) in excess of 160cm would be required for hydrostatic pressure to form the funnelled shape in the xrays from two 1997 studies. A column of urine 160 metres high would be needed for hydrostatic pressure to open out the urethra

Bush M.B, Moron C, Messner-Pellenc L, Petros PE, Millard R. A mechanical model for the opening of the human female urethra. Proceedings of Biomedical Engineering 2005, Austria, K.-P. Adlassnig and M. Bracale (eds), Acta Press, 2005:210-213.

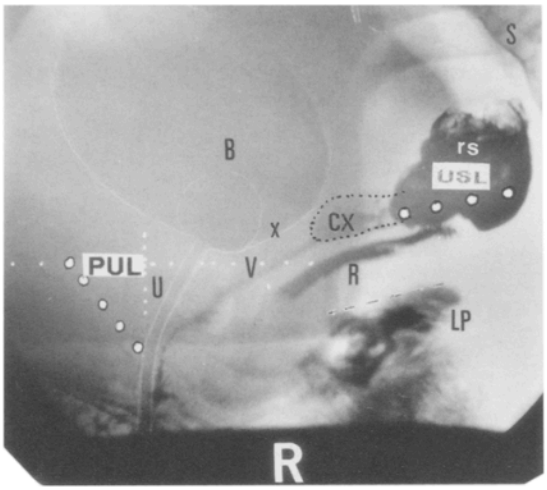

Fig. 1. Resting position of pelvic organs, normal patient. Continent patient, sitting. This is a sitting lateral X-ray in the resting position with a full bladder (B) incorporating a Foley catheter; radio-opaque dye has been injected into the Foley balloon, vagina (V), rectum (R) and levator plate (LP); superior border of LP = broken lines; the anterior diagonal line composed of small solid circles represents pubourethral ligaments (PUL), and the posterior circles the uterosacral ligaments (USL). CX = cervix; U = urethra; X = insertion point of bladder base to vagina; S = sacrum; 'rs' = ballooned area in the rectum; the intersecting white dotted horizontal and vertical lines are reference lines for organ movement drawn from fixed bony points.

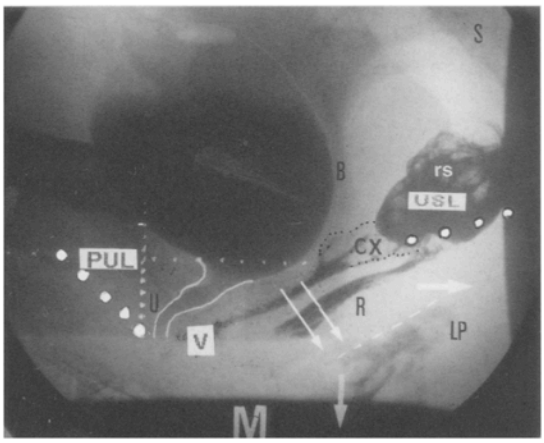

Fig. 2. Micturition. With reference to Fig. 1 (same patient), the vagina (V) and bladder base appear to have been stretched open ('funneled') by a backward force (arrow); the anterior edge of LP is angulated downwards, apparently by a downward force (arrow); 'funneling' bladder neck is consistent with having been caused by (external) pelvic floor muscle forces [15]. Labeling otherwise as per Fig. 3.

The 1997 studies

Petros PE, Ulmsten U. Role of the pelvic floor in bladder neck opening and closure: I muscle forces. Int Urogynecol.J 1997;8:74-80.

Petros PE, Ulmsten U. Role of the pelvic floor in bladder neck opening and closure: II vagina. Int Urogynecol J 1997;8:69-73

Reviewer A - Comment 7: 2nd "USLs are weak, the LP/LMA muscles which contract against them weaken, and the system becomes unbalanced. Compensatory forward-acting closure muscle action by PCM narrows the distal urethra. The detrusor expulsion pressure needs to rise, and the patient experiences symptoms of

"underactive bladder". Perhaps a better description is "obstructed micturition".

This is a very confusing statement for two reasons: first: the authors confuse voiding symptoms with the diagnosis of underactive bladder.
According to the international Continence Society detrusor underactivity is defined as "a contraction of reduced strength or duration resulting in prolonged bladder emptying or a failure to achieve complete bladder emptying". Besides, the authors confuse detrusor underactivity with bladder outlet obstruction (BOO). The mechanism the authors propose to explain why a weak USL causes a voiding dysfunction would fit better with a BOO.

Reply: There is no confusion if one looks at the situation via the IT. The IT views symptoms as what the patient perceives when the outflow tract cannot be opened externally from "C" closed to "O" open, figure2. which is perceived by the patients as an obstruction to emptying. The IT explains weaker LP/LMA contractions exactly as per ICS definitions. See lower graph in figure 4. Symptoms are

(M,P)	**SYMPTOMS OF DEFICIENT EMPTYING**
(M,P)	Do you feel that your bladder isn't emptying properly?
(M,P)	Do you ever have difficulty starting off your stream?
(M,P)	Is it a slow stream?
(M,P)	Does it stop and start involuntarily?

These symptoms improve to various degrees after USL repair (In the 1997 paper (see below), the results were emptying symptoms 50% (n = 65) mean residual urine >50 ml from 110 ml to 63 ml, P = <0.02...
The outlet is "relatively obstructed" , because the posterior opening forces LP/LMA, cannot (externally) open out the urethra from "C" closed to "O" open, (broken lines, figure2).

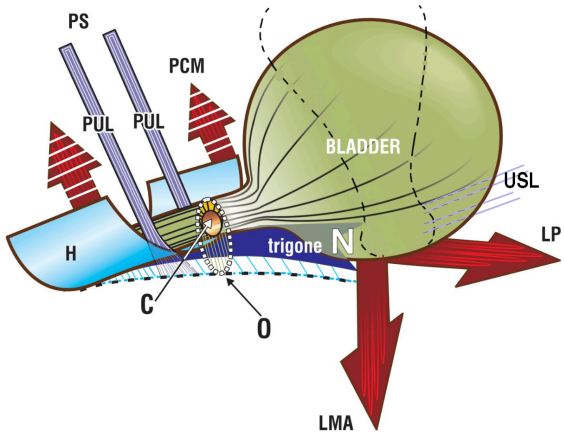

Figure 2 The opposite directional vector forces are always in balance in the normal patient. During micturition, PCM relaxes. LP/LMA contract to open out the posterior wall of the urethra. The posterior vectors LP/LMA, require a firm uterosacral ligament (USL) insertion point. If USL is loose, the

posterior vectors weaken, and the LP/LMA cannot adequately open out the posterior wall of urethra from “C” closed to “O” open (broken lines). PCM=pubococcygeus muscle; LP=levator plate; LMA=conjoint longitudinal muscle of the anus; PUL=pubourethral ligament; O=open urethra; C=closed urethra; N=stretch receptors; H=suburethral vaginal hammock.

Reviewer A - Comment 8: However, the relationship between BOO and weak USL is highly speculative and not based on any experimental study.

Reply: We rely on post-operative improvement UDS parameters Here is post-operative urodynamic data from a 1997 study following pubourethral and uterosacral ligaments slings- see abstract

Petros PE. New ambulatory surgical methods using an anatomical classification of urinary dysfunction improve stress, urge and abnormal emptying. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(5):270-7. doi: 10.1007/BF02765483. PMID: 9557990.

Abstract: The aim of the study was to introduce an anatomical classification for the management of urinary dysfunction based on the Integral Theory, a new connective tissue theory for female incontinence. Eighty-five unselected patients, aged 27-83 years, 12 with pure stress symptoms and 73 with mixed incon- tinence symptoms, were classified as having laxity in the anterior, middle or posterior zones of the vagina, using specific symptoms, signs and urodynamic parameters summarized in a pictorial algorithm. Special ambulatory surgical techniques, which included the creation of neoligaments, repaired specific connective tissue defects in the anterior (intravaginal slingplasty (IVS), n = 85), middle (cystocele repair, n = 6), or posterior zones (uterine prolapse repair, n = 31, or infracoccygeal sacropexy, n = 33). Almost all patients were discharged within 24 hours of surgery, without postoperative catheterization, returning to fairly normal activities within 7-14 days. At (mean) 21-month follow-up cure rates were: stress incontinence 88% (n = 85), frequency 85% (n = 42), nocturia 80% (n = 30), urge incontinence 86% (n = 74), emptying symptoms 50% (n = 65). Mean objective urine loss (cough stress test) was reduced from 8.9 g preoperatively to 0.3 g postoperatively, and mean residual urine >50 ml from 110 ml to 63 ml, P = <0.02. Pre- and postoperative urodynamics indicated that detrusor instability was not associated with surgical failure. Two new directions, based on the Integral Theory, are presented for the management of female urinary dysfunction, an anatomical classification which delineates three zones of vaginal damage, and a series of ambulatory surgical operations which repair these defects. The operations are fairly simple, safe, effective and easily learnt by any practising gynecologist

See also “Abnormal bladder emptying” (n=24) from Table1 below from Petros P, Abendstein B, Swash M. Uterosacral ligament repair improves urinary retention and other Fowler's syndrome descriptions. Cent European J Urol. 2018;

in particular, symptom improvement, reduction in voiding time, increase in natural voiding volume.

Table 1. *Pre-operative and post-operative results (after TFS reinforcement of USLs) in 24 women with posterior fornix syndrome*

	Pre-op	Post-op	P value
PVR	272 ml (100–630)	34 ml (0–150)	<0.0001
Abnormal bladder emptying (24 patients)	100%	9 100% cured 9 80% cured 2 50% improved 3 failed	<0.0001
Natural bladder volume	Mean 598 ml	Mean 301 ml	0.0001
Voiding time	Mean 50 sec	Mean 20 sec	0.006
Peak urine flow rate	42 ml/sec	37 ml/sec	NS
Chronic pelvic pain VAS scale assessment	18/24	14 improved 80%	<0.0001
Max urethral closure pressure (4 patients)	>93 cm water	75 cm water	NS
Urge	17/24 3–4 wet episodes/day (range 1–8/day)	13/17 cured 3 episodes/day range (1–8) in 4 patients	<0.0015
Frequency	Mean 12/day (range 5–21) 14 voided >14 times/day	Mean 8.5/day (range 5–13) 8 voided > 8/day	0.015
Nocturia	2 or more/night in all 24 patients. Mean 4.6 (range 2–9)	13 cured. 10 failures mean 2.7/night (range 2–6). 1 lost to F/U.	<0.0001
Excess detrusor activity	4 patients	1 patient	–

Reviewer A - Comment 9: The levator ani complex of which the pubococcygeus muscle is one of its layers can effectively affect micturition phase by reflex contraction during voiding.
Reply: YES

This condition is known as detrusor external sphincter dyssynergia (DEED) and is due to an involuntary reflex to prevent involuntary detrusor contraction.
Reply: YES

According to the IT, there is a battle between the closure reflex and the micturition reflex. There is no evidence of USL participation in this mechanism.
Reply: There must be, given the improvement in symptoms and urodynamic parameters after USL repair, Table 1 above.

See also feedback control mechanism Petros PE. Detrusor instability and low compliance may represent different levels of disturbance in peripheral feedback control of the micturition reflex. Neurourol Urodyn. 1999;18(2):81-91. doi: 10.1002/(sici)1520-6777(1999)18:2<81::aid-nau3>3.0.co;2-z. PMID: 10081947.

Reviewer A - Comment 10: 3rd "In a normal woman, once the urine starts flowing, the urine in the urethra being incompressible, resists the elastic closure forces of the urethra and surrounding tissues and removes the need for the pelvic muscles to continue to contract".

This is another erroneous statement. The urethra does not become incompressible

after the urine stars flowing. In fact, it is the elastic properties of the urethra which justify its behaviour during the voiding phase as Werner Schaefer has shown, the urethra behaves as a compressible structure with a flow-regulating zone located in the membranous urethral known as the flow controlling zone. Furthermore, the pelvic muscles relax during voiding under physiological conditions. In fact, their contraction is a pathological condition as I have said above known as DEED.

Reply: "This is another erroneous statement." It is a concern when someone makes a categorical statement , especially when the statement is explained in the text.
Reply to "Werner Schaefer has shown, the urethra behaves as a compressible structure with a flow-regulating zone ". Xray, figure3, shows the opposite. The urethra is actually opened out.

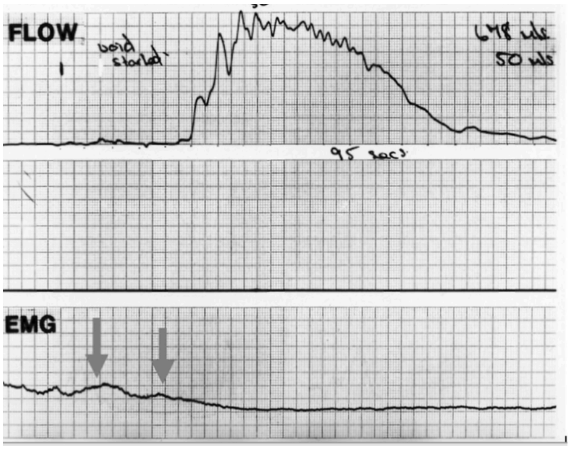

Figure 4 The chart shows normal flow. The EMG in vaginal fornix shows pelvic muscle contraction before urine flow starting and ceases once flow is established. The explanation for pelvic contraction ceasing after urine is in the urethra is that water is incompressible; the bladder smooth muscle spasms until the bladder is completely empty

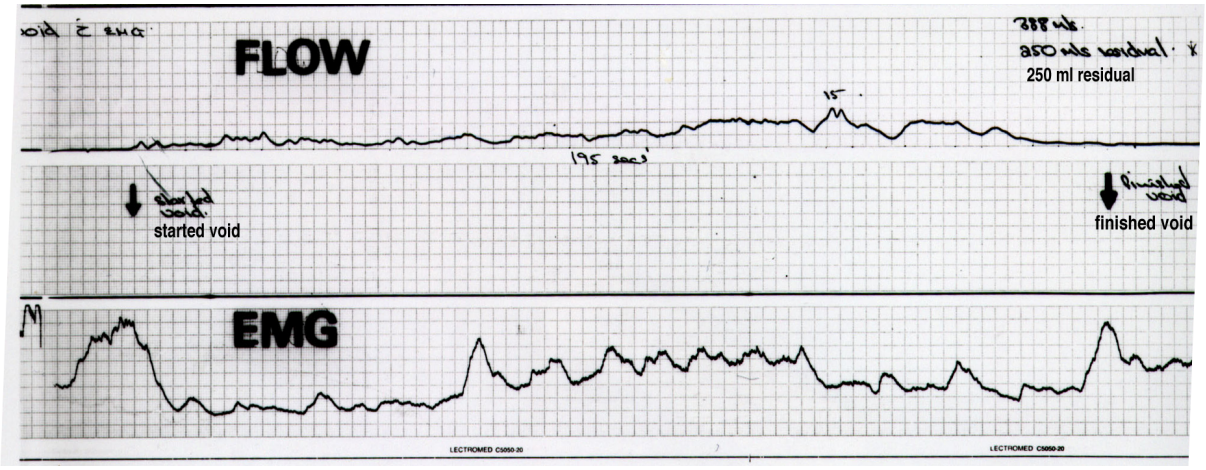

Figure 5 Compared to Figure 4, the chart shows slow urine flow "stopping and starting" pattern. The EMG in vaginal fornix shows the pelvic muscles repeatedly contracting to try and open the urethral tube, not so successfully as the flow is very slow and prolonged, indicating detrusor contraction against an unopened urethra.

Reviewer A - Comment 11: "Furthermore, the pelvic muscles relax during voiding under physiological conditions".

Reply: Please refer to EMG. The posterior pelvic muscles actually contract to initiate expulsion of urine. We know for a 1993 urodynamic study that the muscles which close the distal urethra, PCM (pubococcygeus muscles) relax immediately prior to micturition.

See Petros PE, Ulmsten U. Bladder instability in women: A premature activation of the micturition reflex. Neurourol Urodynam. 1993;12:235-239 .

Reviewer A - Comment 12: 4th "Opening out of the outflow tract exponentially lowers the urethral resistance to flow, inversely by the 4th power of the radius (Poiseuille's Law").
This is another mistake. The fluid dynamics of the urethra do not fit the Poiseuille's laws because urine flow is not turbulent but rather laminar under physiological conditions. Bernoulli's equation better fits its behaviour during voiding phase.

1. **Reply: "**Bernoulli's equation better fits its behaviour during voiding phase". Bernoulli's equation is based on constant flow. It is evident from figure4 and most certainly, figure5, that urine flow during micturition is not constant. Our bench experiments Bush MB, Petros PEP, Barrett- Lennard BR. On the flow through the human urethra. Biomechanics. 1997;30(9):967-969. did approximately fit Poiseuille's Law. From studies 1&2 below**,** we know that over a 4cm distance, we found that the flow was turbulent. In the mathematical model paper, Petros PE, Bush MB. A mathematical model of micturition gives new insights into pressure measurement and function. Int Urogynecol J. 1998;9:103-107., we used the formula

$$\Delta P = P_{ves} - P_0 = \frac{8\rho Q^2 L f}{\pi^2 d^5} + \frac{1}{2}\rho V^2 - \rho g \Delta h$$

where the pressure difference ΔP is the difference between the intravesical pressure P_{ves}, and the pressure acting at the tube exit P_0. Q is the volume flow rate, ρ is the fluid density, g is the acceleration due to gravity, f is the frictional factor, and Δh is the change in height of the urethra from one end to the other (approximately 2 cm).

The chart below is from ref 2 below graphically expresses the above formula which showed non-laminar flow exponentially determined.

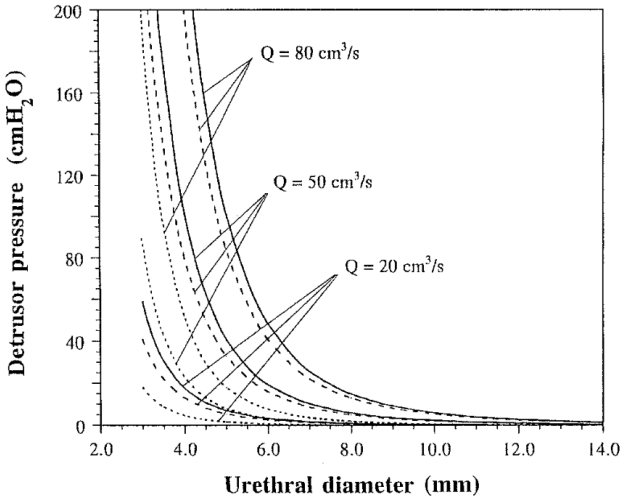

Fig. 4. Detrusor pressure as a function of the urethral diameter. For a tube length of 4 cm. . . . . , frictional component; - - - - - -, dynamic component; ————, total.

Reviewer A - Comment 13: Actually**,** on the other hand, assuming that the above premises were not incorrect. This is not enough reason to prove the theory is correct. Contrary to a formal theory like in mathematics or logical, factual sciences like physiology must prove their theories empirically. Unfortunately, in their paper the authors do not refer to any published study showing that the SCI repair improves BOO or UAB.

Reply: The foregoing data, xray studies, bench experiments, urodynamic studies is from empirical physiological data.

Reviewer A - Comment 14: They only refer to uncontrolled studies reporting that after USL laxity repair patients improved urinary symptoms, but as I have stated above BOO and UAB are both urodynamic conditions whose diagnosis requires urodynamic tests.

Reply: The 1997 and 2010 studies were urodynamically controlled for urodynamic DI (now DO) and urine flow. Petros PE. New ambulatory surgical methods using an anatomical classification of urinary dysfunction improve stress, urge and abnormal emptying. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(5):270-7. doi: 10.1007/BF02765483. PMID: 9557990. of 85 women was urodynamically controlled, pre and post-operatively as was the 2010 study Petros PEP, Richardson PA. TFS posterior sling improves overactive bladder, pelvic pain and abnormal emptying, even with minor prolapse –a prospective urodynamic study. Pelviperineology. 2010;29:52-55

See tables below – pre and post-op data.

TABLE 1. – Sympton Outcome - 67 patients.

	Symptom change with surgery			% cure in brackets	
Fecal Incontinence	Frequency >10/Day	Nocturia >2/night	Urge incontinence >2/Day	Abnormal emptying	Pelvic pain
n=23 (87%) P<0.005	n=27 (63%) P<0.005	n=47 (83%) P<0.005	n=36 (78%) P<0.005	n=53 (73%) P<0.005	n=46 (86%) P<0.005

TABLE 2. – Sympton Outcome - 1st degree vault/uterine prolapse (n=28).

	Symptom change with surgery			% cure in brackets	
Fecal Incontinence	Frequency >10/Day	Nocturia >2/night	Urge incontinence >2/Day	Abnormal emptying	Pelvic pain
n=8 (100%)	n=8 (63%)	n=17 (76%)	n=17 (76%)	n=19 (73%)	n=18 (82%)

TABLE 3. – Pre-operative urodynamic "Overactive Bladder"

Patient	1	2	3	4	5	6	7	8
Pre-op 24 hr pad test (gm)	7	14.3	6.5	272	522	910	2100	644
Post-op 24 hr pad test (gm)	0	0	0	70	20	13	*1980	720

*asterisk indicates detrusor instability post-operatively also

Reviewer A - Comment 15: Finally, I would like to add two suggestions. The first is that the authors' work is based on Petros' pelvic floor theory. This theory is excellent for explaining pelvic floor disturbance in terms of stress urinary incontinence and pelvic floor prolapse, but it cannot explain voiding phase dysfunctions.

Reply: This the reviewer's opinion. We believe the data we have presented go some considerable way towards answering the reviewer's questions. It is good to see the parts of the Integral Theory paradigm concerning "urinary incontinence and pelvic floor prolapse" acknowledged by the reviewer. Since 1990, the IT has extended further to OAB ("overactive bladder syndrome) and UAB (underactive bladder syndrome).

https://obgyn.onlinelibrary.wiley.com/toc/16000412/1990/69/S153

We welcome further comments from the reviewer on the evidence provided here.

Reviewer B

For author

This is an interesting concept.

For editor

Sorry is this a commissioned review? in which case should it not be reviewed by the in-house editorial team?

If it is not an invited review then it appears to be a brief review article of a novel

concept but it does not really add anything new to the knowledge base.
I couldn't open a video.

Reply: Dear reviewer B. Thank you for taking the time to review this paper. It is indeed “A brief review article of a novel concept but it does not really add anything new to the knowledge base”.