Peer Review File

Article information: https://dx.doi.org/10.21037/atm-23-1769

Review Comments

Reviewer A

Reviewer A's Comments: A very interesting paper and I completely agree with the integral theory. The figures are very good.
Could the authors explain which techniques (without mesh) could be used to repair cystocele? Same question with rectocele? Same question with apical prolapse? What do you think about anterior sacrospinofixation?
Is it possible to have a surgical video of the technique of Prof. Petros?
The authors were instructed to confine their comments to the Integral Theory principles of surgery.

Reply: We thank Reviewer A for his/her comments. Detailed surgical technique and videos for each of these operations are described in paper No. 15 "Wide-bore polyester sutures create new collagen for cure of prolapse and incontinence without need for tapes."

Reviewer B

Reply: We thank Reviewer B for a detailed and forensic analysis, the mark of a rigorous scientific approach, which was much appreciated. It obliged us to provide the data to support our comments.
The aim was to outline the surgical principles based on the theory. Several techniques are analysed. Comparison is made between methods which follow the ITP and other methods. It was not possible to cover every point in a complex subject, especially as the authors had to follow a template with a limited word count.
We agree with many of the comments, but differ in others. Where we disagree, we have done so in blue type.

Comment 1: The goal of the article is to share surgical principles developed by a group of surgeons who believe that the follow the "integral theory paradigm" of surgical repair. The premise is based on conjecture that collagen leeches from the pelvic supportive ligaments with age and retrospective studies from a single center showing that a tissue fixation system that utilizes collagen containing "tapes" are associated with optimal long term outcomes in Japanese women.

Reply: Conjectural unfortunately implies without proof. It is a fact that collagen breaks down after the menopause. Here are two basic science studies.

Sone T, Miyake M, Takeda N, Fukunaga M. Urinary excretion of type I collagen crosslinked N-telopeptides in Healthy Japanese adults: Age- and sex-related changes and reference limits. *Bone.* 1995;17:335–339. [PubMed] [Google Scholar].
Goepel C. Differential elastin and tenascin immunolabeling in the uterosacral ligaments in postmenopausal women with and without pelvic organ prolapse. *Acta Histochem.* 2008;110:204–209. [PubMed] [Google Scholar]

The Japanese paper was an example. There are many other papers

Here is one by Liedl et al, 611 patients and many others.

Liedl B, Inoue H, Sekiguchi Y, et al. Is overactive bladder in the female surgically curable by ligament repair? Citation: Cent European J Urol. 2017; 70: 51-57.

Petros PE. New ambulatory surgical methods using an anatomical classification of urinary dysfunction improve stress, urge and abnor- mal emptying. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(5):270–7.

Goeschen K. Posterior Fornix Syndrome: Comparison of original (2004) and modified (2015) post-PIVS anatomic and symptomatic results: a personal journey. Pelviperineology. 2015;34:85–91.

Petros P, Richardson PA. TFS posterior sling improves overactive bladder, pelvic pain and abnormal emptying, even with minor pro- lapse. A prospective urodynamic study. Pelvi- perineology. 2010;29:52–55.

Inoue H, Kohata Y, Sekiguchi Y, et al. The TFS Minisling restores major pelvic organ Pro- lapse and symptoms in aged Japanese women by repairing damaged suspensory ligaments – 12–48 month data. Pelviperineology. 2015; 34:79–83.

Goeschen K, Gold D. Surgical cure of chronic pelvic pain, associated bladder & bowel symp- toms by posterior sling in 198 patients vali- dates the Pescatori Iceberg principle of pelvic symptom co-occurrence. Pelviperineology. 2017;36:84–88.

Wagenlehner F, Müller-Funogea IA, Perletti G, et al. Vaginal apical prolapse repair using two different sling techniques improves chronic pelvic pain, urgency and nocturia – a multicentre study of 1420 patients. Pelviperi- neology. 2016;35:99–104.

Inoue H, Kohata Y, Fukuda T, Monma M, Uzawa Y, Kubo Y, et al. Repair of damaged ligaments with tissue fixation system minisl- ing is sufficient to cure major prolapse in all three compartments: 5-year data. J Obstet Gynaecol Res. 2017 Oct;43(10):1570–7.

Haverfield M. Tissue Fixation System (TFS) neoligament pelvic organ repair procedures – 12 and 24 month results. Pelviperineology. 2015;34:70–74.

Richardson P. Surgical cure of nocturia using 4 different methods based on strengthening the structural supports of the vaginal apex – a short review. Pelviperineology. 2015;34:92–93.

Petros PE, Liedl B, Gold D. Should surgeons continue to implant mesh sheets behind the vagina? Int Urogynecol J Pelvic Floor Dys- funct. 2018 Jun;29(6):777–9.

Caliskan A, Goeschen K, Zumrutbas AE. Long term results of modified posterior intra-vaginal slingplasty (P-IVS) in patients with pelvic organ prolapse. Pelviperineology. 2015; 34:94–100.

Abendstein B, Brugger BA, Furtschegger A, Rieger M, Petros PE. Role of the uterosacral ligaments in the causation of rectal intussus- ception, abnormal bowel emptying and fecal incontinence-a prospective study. Pelviperin- eology. 2008;27:118–121.

Goeschen K. Role of uterosacral ligaments in the causation and cure of chronic pelvic pain syndrome. Pelviperineology. 2015;34:2–20.

Liedl B,Goeschen K,Sutherland SE, Roovers JP, Yassouridis A. Can surgical reconstruc- tion of vaginal and ligamentous laxity cure overactive bladder symptoms in women with pelvic organ prolapse? BJU Int. 2019 Mar; 123(3):493–510. Liedl B, Goeschen K, Durner L. Current treat- ment of pelvic organ prolapse correlated with chronic pelvic pain, bladder and bowel dys- function. Curr Opin Urol. 2017 May;27(3): 274–81.

Müller-Funogea A. Posterior fornix syn- drome: a new urogynecologic entity. Ethio- pathogenesis and proposal for surgical thera- py. Thesis, Romania: Medical University of Bucharest; 2014.

Comment 2: The basis of this approach is to reinforce ligaments that are weakened in the pathogenesis of pelvic organ prolapse and stress incontinence.

It avoids the use of large sheets of mesh and focuses on tapes that elevate the vagina based on DeLancey's levels of connective tissue support to the vagina.

Reply: Yes.

Comment 3: While interesting, the article ignores the critical importance of the pelvic floor musculature.
Indeed, there is accumulating evidence that injury to the pelvic floor at the time of vaginal birth is the sentinel event that leads to prolapse and incontinence later in life and this event places undo stress on the supportive ligaments which have limited supportive capacity.

Reply: Yes.
With respect, we see the 2nd part of the reviewer comments as an unproven hypothesis. Of course muscles are injured, but nowhere to our knowledge is there any study where repair of muscles has led to cure of prolapse.

The one study where this was done reported a 79% failure rate at 18 months

1. Wong V, Shek KL, Korda A, Benness C, Pardey J, Dietz HP. A pilot study on surgical reduction of the levator hiatus: the puborectalis sling. Int Urogynecol J. 2019 Dec;30(12):2127-2133. Available from: doi:10.1007/s00192-019-04062-0. Epub 2019 Aug 6. PMID: 31388717.

In contrast, we respectfully refer the reviewer to the Liedl and also the Japanese paper, both of which reported 90% anatomical cure of the prolapse in 611 women.

Comment 4: This article is purely conjectural. While an interesting concept based on the reduced mesh burden, this reviewer would be more supportive of a prospective randomized trial showing the benefit of these tapes over native tissue repair prior to

the publication of such an article.

Reply: Conjectural unfortunately implies without proof.. The cure rates reported are real. Agree about RCT. However, it would be unethical to do an RCT when Shkarupa's study and PROSPECT STUDIES showed 80% failure rate at 12 months with nAtive tissUe repair in older women. Meanwhile, the Liedl and Inoue studies using tapes to create collagenous neoligaments demonstrated only 10% failure in 70 year old women at 12 months.

Table I Cure rate (%) of POP and overactive bladder symptoms at different points of follow-up.

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

Table 1 from Shkarupa et al Shkarupa D, Zaytseva A, Kubin N, Kovalev G, Shapovalova E. Native tissue repair of cardinal/uterosacral ligaments cures overactive bladder and prolapse, but only in pre-menopausal women. Cent European J Urol. 2021;74(3):372-378. doi: 10.5173/ceju.2021.285.3. Epub 2021 Jun 30. PMID: 34729228; PMCID: PMC8552928.

Comment 5: Moreover, independent of the size of a permanent material, there will always be complications associated with it. This is also true of permanent suture.

Reply: Yes, certainly that is correct. However, the larger the implanted material, the greater the number of complications.

Comment 6: My additional comments are below:

Comment 6.1: The new collagen synthesis is not novel. It is simply related to the

foreign body response to polypropylene. This type of encapsulation is not regenerative or restorative. This should be acknowledged.
Reply: We respectfully disagree. Collagen turns over (regenerates) at regular intervals in the body, from every 6-8 weeks, to 9 months for bone.

Comment 6.2: Polyester suture is woven and will susceptible to bacterial colonization in areas that immune cells cannot penetrate – a monofilament would be a better choice but that has already been explores in the BURCH procedure and uterosacral ligament suspension
Reply: Yes, bacterial colonization is theoretically possible. We have not seen any infections with the wide bore polyester. However, your suggestion for change to monofilament is wise, and we will take it on board.

Comment 6.3: Line 143: what is the evidence for this assertion
Reply: See table1

Comment 6.4: Line 146: one could argue that it is the amount of collagen per tissue region that confers mechanical strength. Removing a segment of a tissue without altering the concentration of its structural proteins would NOT change mechanical properties. On the otherhand, narrowing may place undue tension on lateral structures.
Reply: Yes. Agree to all the above. In table1 above, Shkarupa showed 80% cure rate at 18 months with native tissue repair. Shkarupa also posed the question, "What happens after the menopause in these successful operations, when the collagen breaks down?"

Comment 6.5: Line 148: the data that collagen is lost in the pelvic supportive ligaments with age is weak. Rather collagen stiffens due to crosslinking and glycation end products.

Reply: Yes agree. Crosslinking of the collagen does stiffen, and the collage becomes more brittle. See Shkarupa data at 18 months and references for collagen breakdown. Quote from the 1993 publication of the Integral Theory.

Petros PE, Ulmsten U. An Integral Theory and its Method, for the Diagnosis and Management of female urinary incontinence. Scand J Urol Nephrol. 1993;27 Suppl 153:1-93.

PART II. THE BIOMECHANICS OF VAGINAL TISSUE AND SUPPORTING LIGAMENTS WITH SPECIAL RELEVANCE TO THE PATHOGENESIS OF FEMALE URINARY INCONTINENCE

"Though the collagen fibrils themselves increase in strength with age, a net loss of tissue strength with age has been demonstrated by direct testing "(94) .

Comment. This does seem paradoxical in view of the more intense cross bonding. Perhaps collagen breakdown with age (see Sone paper above) could explain it.

(94) Yamada H. Mechanical properties of urogenital organs and tissues in Strength of Biological Materials, (1970), Williams & Wilkins Co, Baltimore. Ed Evans FG. 205-218.

Comment 6.6: Line 201: again the authors are overlooking the important role of the pelvic floor musculature

Reply: FINALLY The Integral Theory does not disregard the role of muscles. The muscles are fundamental. It is the muscles which open and close the urethra contract against mainly pubourethral and uterosacral ligaments. If the ligaments are weak, so is the force of the pelvic muscle contractions. That is why the theory stated as early as 1990, *"Stress and urge, mainly occur, for different reasons, from laxity in the vagina or its supporting ligaments, a consequence of altered collagen/elastin."*