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Growth Hormone Adjuvant trial for poor responders undergoing IVF



We were pleased to note that the registered randomised control trial from Cairo [1] showed some similar outcomes as our retrospective Australian trials, which were cited by the authors. In particular growth hormone (GH) adjuvant therapy 7.5 IU daily from Day 21 to Trigger (20 days) for poor responders in IVF, generated significantly more usable embryos; meaning embryos which were transferred in the fresh cycle plus embryos deemed suitable for cryopreservation; some of which were later transferred in a frozen embryo transfer (FET) cycle. However, their study failed to show any benefit in the main outcome measures, namely clinical pregnancy and live birth rates, including cumulative live birth rate. However, we find the study faulted, with unrecognised limitations, causing wrong conclusions to be drawn.

Firstly, we believe many of the embryos generated in their study were not given the best opportunity to implant and were wasted by the transfer of up to 3 embryos per fresh cycle. Although unstated we suspect those embryos selected for fresh transfer were the highest quality. However, we would suggest that their luteal phase management using Cyclogest 400 mg twice daily was suboptimal for the poor responder group. We believe that the poor responder group do best with a combination of HCG injections combined with micronized progesterone pessaries 400 mg three times daily [2,3], increasing the dosage further according to mid-luteal serum progesterone levels [4,5] which are measured in a defined mid-range for optimal pregnancy outcomes.

Furthermore, in recent years with the Cryotop Vitrification strategy, we have demonstrated that FET cycles generate higher implantation rates; firstly, using the remaining embryos cryopreserved after the best was transferred fresh. Secondly, this had led us to now cryopreserve the very best embryos for subsequent FET under HRT control [3]. In keeping with the current Australian trend our facility preferentially conducts single embryo transfers (SETs: 95%) and despite fresh transfers of the lesser quality (but suitable) embryos, our facility has pregnancy rates in the highest range of the top quartile for FET cycles according to the annual Australia and New Zealand Assisted Reproduction Database; ANZARD [6].

A further retrospective study from our facility is under review and shows that GH-generated embryos implant at a significantly higher rate in the FET cycles of women categorised as poor prognosis when matched with non-GH embryo FETs. The resultant pregnancies had a significantly higher live birth rate (22/78; 28.2% vs 7/78; 9.0%). This means the total productivity rate from a single oocyte retrieval is highest when more embryos reach cryopreservation, preferably those embryos being of the higher quality. The Cairo group should reconsider

their study by applying a SET strategy to direct more high quality embryos to FET.

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Some anatomical explanations for mesh complications



Managing pain after synthetic mesh implants in pelvic surgery. Toozs-Hobson P, Cardozo L, Hillard T. *Eur J Obstet Gynecol Reprod Biol*. 2019 Jan 9;234:49–52. doi: 10.1016/j.ejogrb.2018.12.037. [Epub ahead of print] Review.

Dear Editor, I found this was an excellent summary of pain after mesh implantation and congratulate the editors on addressing a little visited subject. My comments are based on 30 years' experience in dealing with mesh insertions and complications.

Immediate onset of very severe pain

I agree this must be caused by some sort of direct injury to a nerve. I have only seen such severe pain in only 2 or 3 out of several

* Patient's consent for publication has been confirmed and signed.

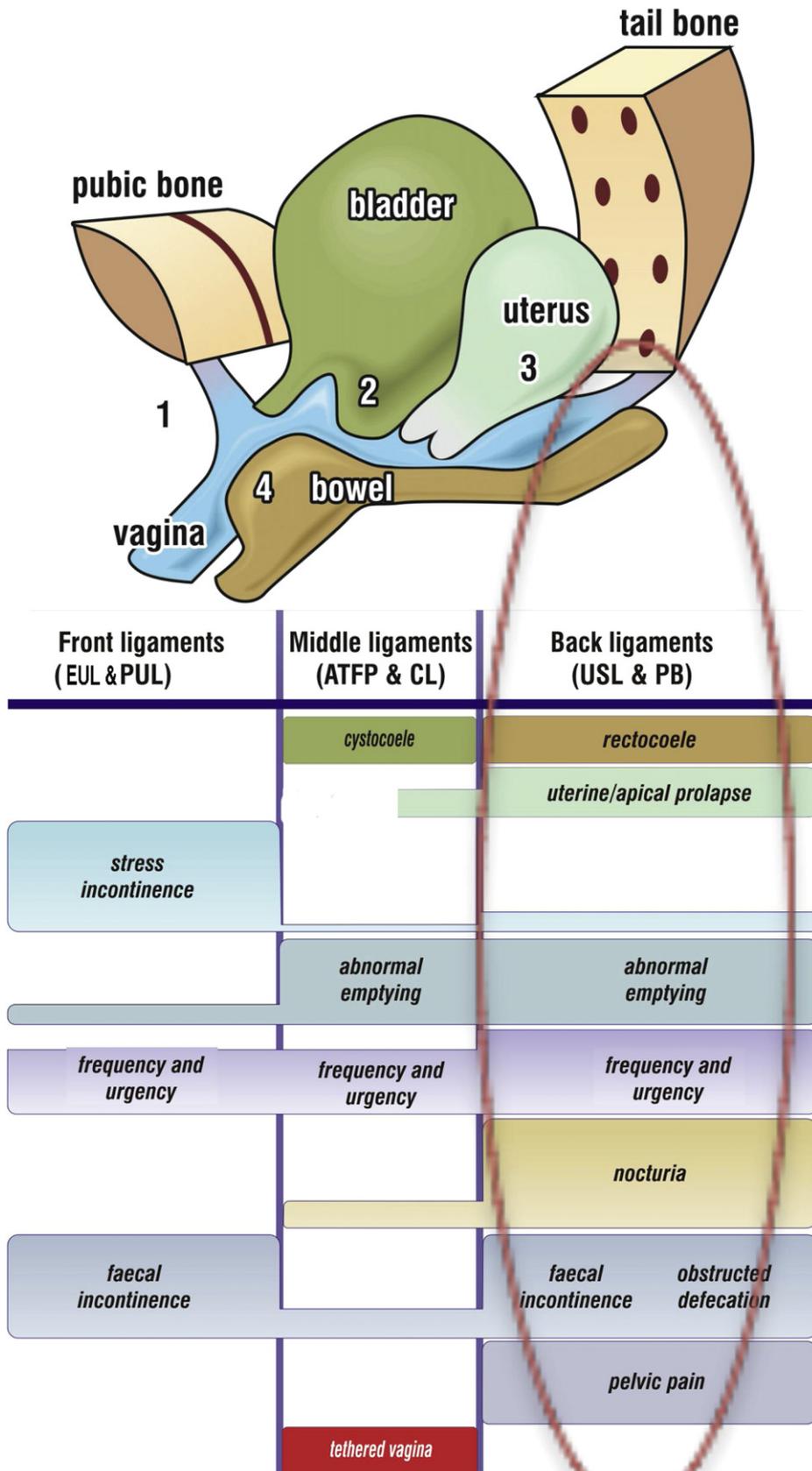


Fig. 1. The Pictorial Algorithm is a summary guide to causation and management of pelvic floor conditions. The posterior zone symptoms with in the ellipse are caused by USL (uterosacral ligament) looseness. PB = perineal body. The numbers in the figure correlate with symptoms or prolapse 1:stress urinary incontinence; 2: cystocele; 3: uterine prolapse; 4:rectocele.

NOTE Major symptoms may occur with minimal ligament damage.

thousand midurethral slings. It settled immediately the tape was removed. Far more common is a lesser post-operative pain seen immediately after mesh surgery in the posterior fornix of the vagina. Like the pain we see with sacrospinous fixation, it disappears within days or weeks.

Delayed presentation weeks or months after surgery

If besides pain, such women also other de novo posterior symptoms such as urge, nocturia, emptying problems, Fig. 1, the pain may be caused by dislocation of the uterosacral ligaments. It is especially evident in post-menopausal women and women with prior hysterectomy. We use the concurrence of other symptoms, Fig. 1, to diagnose this type of pain which is caused by diversion of intraabdominal pressure to dislocate the uterosacral ligaments (USL) as the cause. The other symptoms are generally not volunteered [2]. In premenopausal women, USLs can be repaired by plication [3], which also cures or improves the other symptoms. In older women, OH proline excretion studies indicate their collagen breaks down post-menopausally, and leaches out of the ligaments. Such women need a posterior sling [4]. Pain originating from loose USLs was first described by Gerhard Martius in 1938 [5].

Longer term delayed presentation

If posterior zone symptoms, Fig. 1, co-occur, they may respond to USL repair. If there are no accompanying symptoms, we need to suspect mesh entrapment. We have histology from mesh sheet removals which shows nerves inside the mesh.

Late presentation, years after insertion

These present in several ways including pain, discharge and infections. I have seen such patients 10 years after implantation, more numerous in densely knitted tapes or meshes. Almost invariably these mesh rejections are caused by inflammation due to tissue reaction. These are not infections. They are an immunological rejection, like a splinter, painful but not dangerous. The abscess contains sterile pus. The patient is afebrile. Bacteria are never grown. WCC is normal. Sometime the erythrocyte level is raised. If the patient is febrile, then it is an infection and must be treated as a semi-emergency. The tape has to be removed. Urethral

“erosions” and surfacings are really inconsequential and can be dealt with in the outpatient clinic. Just gently pull up and snip. No LA is needed.

A major difference between tapes and mesh sheets covering the vagina

Mesh sheets which cover the vagina work by blocking descent of prolapse; they fibrose vagina to diminish elasticity. This can cause major uncontrollable urine loss, classically on getting out of bed in the morning or off a chair (Tethered Vagina Syndrome). Cure is by insertion a skin graft to the bladder neck area of vagina to restore vagina elasticity. In contrast, tapes implant far less mesh and correct prolapse by reinforcing ligaments. They connect the organs directly to the skeleton, with minimal contact with vagina, largely avoiding Tethered Vagina complications.

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