The Future of Female Urology

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Disclosures

- Medtronic: Consultant
- Symptelligence: Consultant
- Tengion: Consultant

The Issues

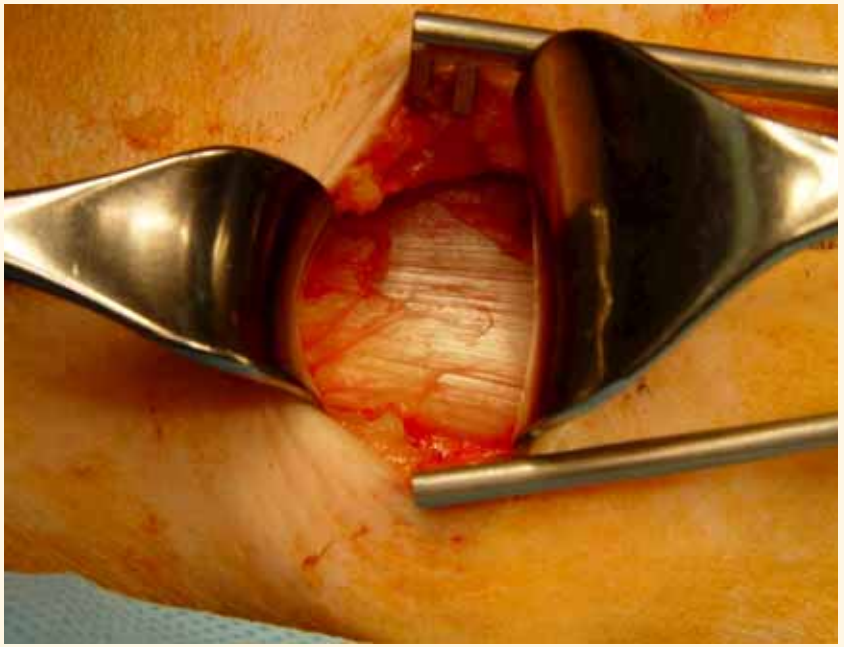
- Stress Urinary Incontinence
  - 1 in 5 women have some degree of SUI
  - >100K sling procedures each year
- Pelvic Organ Prolapse
  - 11% of women will have surgery for POP in their lifetime

Options for Surgical Repair

- Native tissue repair without a graft
  - Anterior colporrhaphy
  - Burch
  - MMK
- Graft procedure
  - Autologous: rectus fascia, fascia lata
  - Xenograft: Pelvicol™, SIS, bovine pericardium
  - Cadaveric: fascia lata, dura mater
  - Synthetic: Type 1-4

Sling Cystourethropexy: Autologous

- Fascia lata, rectus fascia, vaginal wall
- Success rate: 85-93%
- 47% able to walk freely without pain immediately postop
- 93% pain free at 1 week postop
- No infection
- No thrombotic complications



Sling Cystourethropexy: Xenograft

- Xenograft: Pelvicol™, SIS, bovine pericardium
- Success rate: 85%
- Side effects: foreign body reaction

Sling Cystourethropexy: Allograft
Cadaveric Fascia

- Autolysis
- Disease transmission: viral (HIV, Hep C), bacterial, and prion

Cadaveric Fascia Lata Autolysis

- 67 sacrocolpopexy
- 35 sling cystourethropexy

Freeze dried irradiated

- 13 recurrent symptoms <4 months
- 7/13 graft remnant: attenuated, lax
- 6 absent

Fitzgerald et al. AJOG 1999

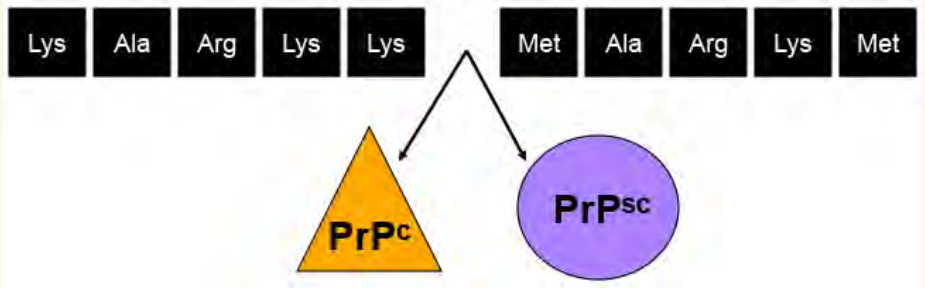
Cadaveric Fascia Lata Autolysis

- Cadaveric Fascia Lata
  - N=121
  - 7 failed < 1 month
- Autologous Fascia Lata
  - N=46
  - 0 failures

Brown et al. JU 2000

Creutzfeldt-Jakob Transmission

Source of Infection	No. cases	Mean incubation period, y (range)	Clinical signs†
Dura mater graft	228	12 (1.3–30)	Cerebellar, visual, dementia
Neurosurgical instruments	4	1.4 (1–2.3)	Visual, dementia, cerebellar
Stereotactic EEG needles	2	1.3, 1.7	Dementia, cerebellar
Corneal transplant	2	1.5, 27	Dementia, cerebellar
Growth hormone	226	17 (5–42)‡	Cerebellar
Gonadotropin	4	13.5 (12–16)	Cerebellar
Packed red blood cells§	3	6.5, 7.8, 8.3	Psychiatric, sensory, dementia, cerebellar



Prion Chemistry

Brown et al. Emerg Infect Dis 2012

Meshes and Grafts used in Pelvic Reconstructive Surgery

Biological grafts

Autografts
- Fascia lata
- Rectus sheath

Allografts
- Fascia lata
- Dura mata

Xenografts
- Porcine
- → Small-intestine submucosa
- → Dermis (Pelvicol)

Synthetic mesh

Absorbable
- Polyglactin (e.g. Vicryl)

Nonabsorbable

Type I: macroporous mesh
- Polypropylene, Polyvinylidene fluoride
- e.g. Prolene, TVT, Monarc

Type II: microporous mesh
- Polytetrafluoroethylene
- e.g. Goretex

Type III: macroporous and microporous or multifilament
- e.g. Mersilene, Teflon, IVS

Type IV: submicronic pore size
- e.g. silicone, silicone-coated mesh

Sling Success Rates

SUPPLEMENTARY TABLE 3

Evidence profile for pubovaginal sling vs midurethral sling

							Summary of findings		
Outcome	**No. studies**	**Total n**	**Methodological quality**	**Consistency**	**Directness**	**Other considerations**	**Evidence strength**	**Effect**	**Outcome importance**
Objective cure	3	233	1B (-1), 1B (-2), 1C(-2)	0	0	0	Low	No difference	Critical
Subjective cure	4	305	2B (-2), 1C (-2)	0	0	0	Very low	No difference	Critical
Perioperative outcomes	4	383	2B (-1), 2C (-2)	-1	0	0	Low	Favors midurethral	Variable
Quality of life	3	342	2B (-1), 1C (-2)	0	0	0	Low	No difference	Critical
Sexual functioning	0	0	NA	NA	NA	NA	NA	NA	High
Total	5 separate studies								

Quality of overall evidence: low. Balance of benefits and harms: comparing PVS (fascia or synthetic material) to synthetic midurethral slings (only retropubic passage was studied), objective and subjective cure outcomes as well as quality of life and sexual function outcomes showed no differences. There were not enough studies available to perform a metaanalysis for objective cure outcomes, but a metaanalysis for subjective cure significantly favored midurethral slings. Both short-term (perioperative) and long-term adverse event data in general favored midurethral slings although metaanalysis did not show a difference for selected adverse-event outcomes.

NA, not applicable; *PVS*, pubovaginal slings.

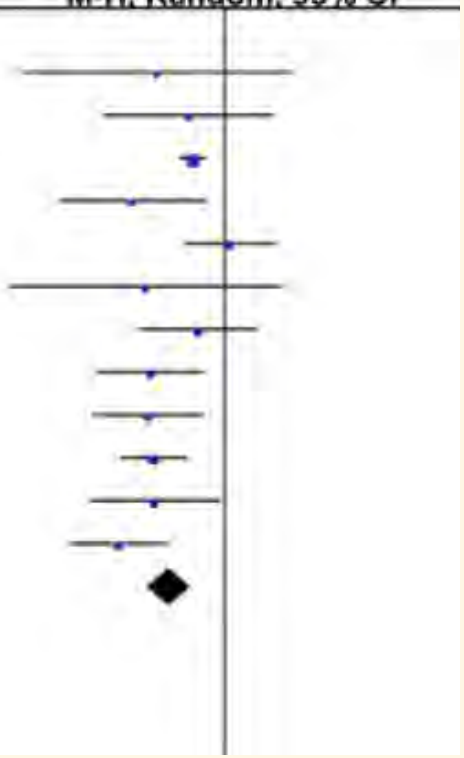
Schimpf. Sling surgery for stress urinary incontinence. Am J Obstet Gynecol 2014.

Efficacy of Mesh or Grafts in Surgery for Vaginal Wall Prolapse (RCTs)

Study or Subgroup	Experiment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 nonabsorbable synthetic mesh VS none						
Al-Nazer 2007	1	20	3	20	0.9%	0.33 [0.04, 2.94]
Ali S 2006	3	46	5	43	2.1%	0.56 [0.14, 2.21]
Altman D 2011	69	176	114	174	12.3%	0.60 [0.48, 0.74]
Del Roy C 2011	3	39	13	39	2.7%	0.23 [0.07, 0.75]
Duggan P	9	19	7	16	5.4%	1.08 [0.52, 2.25]
Dyer K 2010	1	27	3	23	0.9%	0.28 [0.03, 2.55]
Hitunen R 2007	7	104	9	86	3.8%	0.64 [0.25, 1.66]
Menefee SA 2011	5	28	14	24	4.3%	0.31 [0.13, 0.73]
Nguyen JN 2008	5	38	17	38	4.2%	0.29 [0.12, 0.72]
Nieminen K 2010	14	105	40	97	7.5%	0.32 [0.19, 0.56]
Sivaslioglu AA 2008	4	43	12	42	3.3%	0.33 [0.11, 0.93]
Vollebregt A 2011	6	56	34	58	4.9%	0.18 [0.08, 0.40]
Subtotal (95% CI)		**701**		**660**	**52.4%**	**0.41 [0.29, 0.57]**
Total events	127		271			

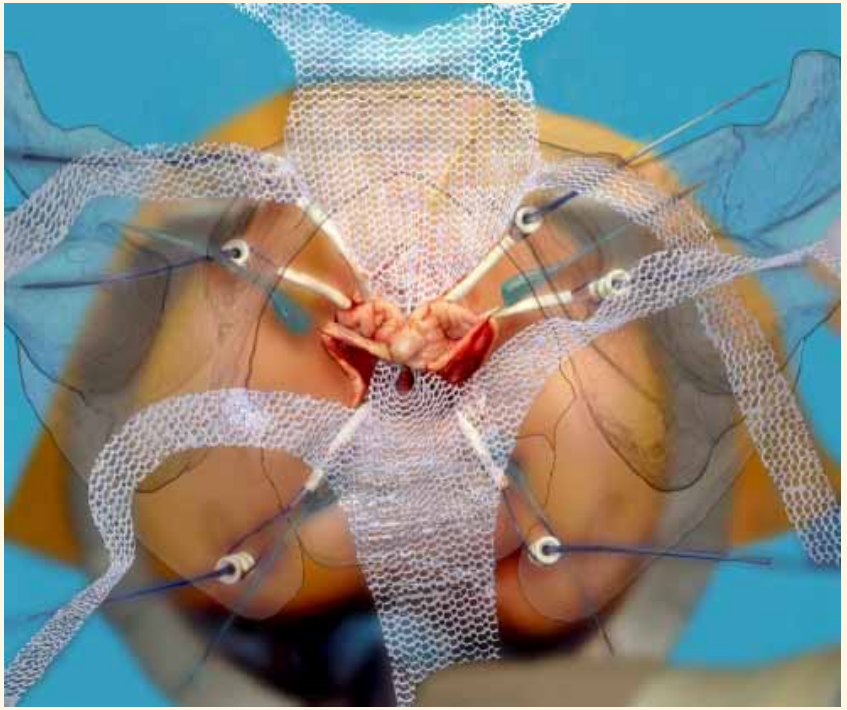
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 23.02$, df = 11 (P = 0.02); $I^2 = 52\%$

Test for overall effect: Z = 5.13 (P < 0.00001)



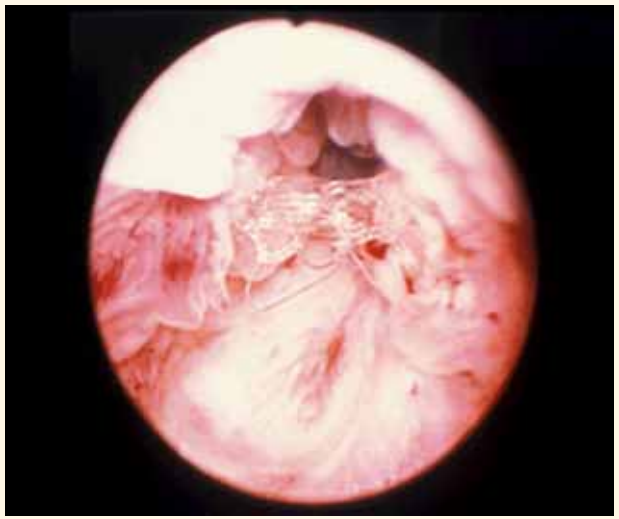
Min et al. Arch Gynecol Obstet 2013

This will not end well



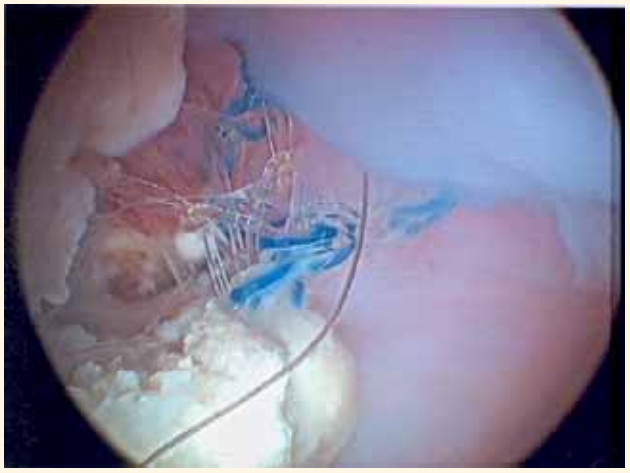
Complications

Perforation

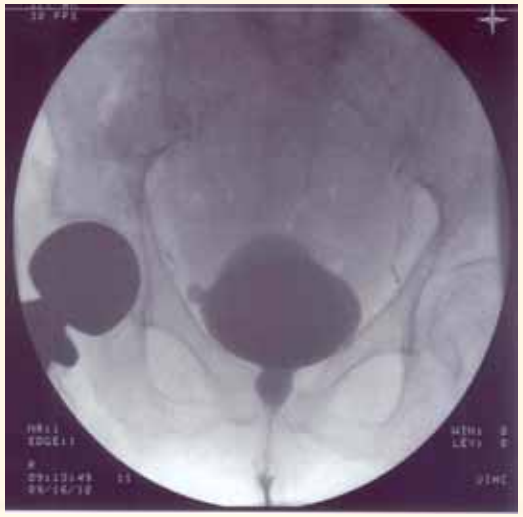


Extrusion

Erosion



Obstruction

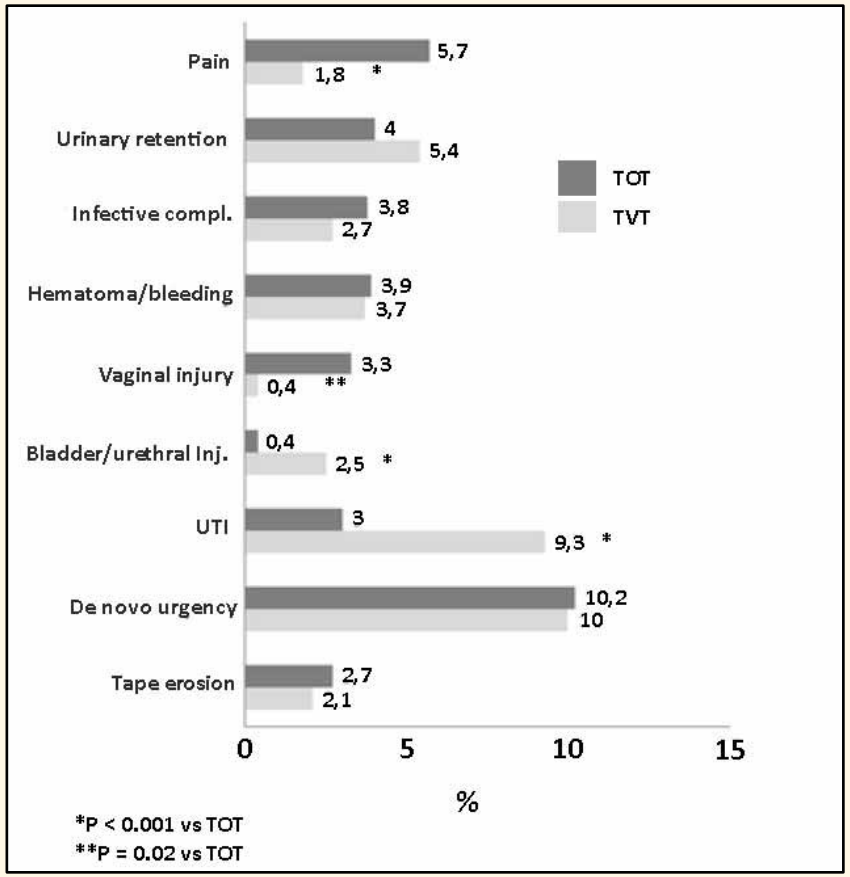


Pain

- Temporally related to mesh placement
- Along the path of the mesh
- Worse with palpation
- Only resolves 28% of the time even with multiple surgeries (Blavias JG et al. J Urol 2013)

Complications of Slings

- Meta-analysis of 49 studies
  - 11 RTCs
- 6,406 pts
- 766 complications RP-MUS
- 579 complications TO-MUS

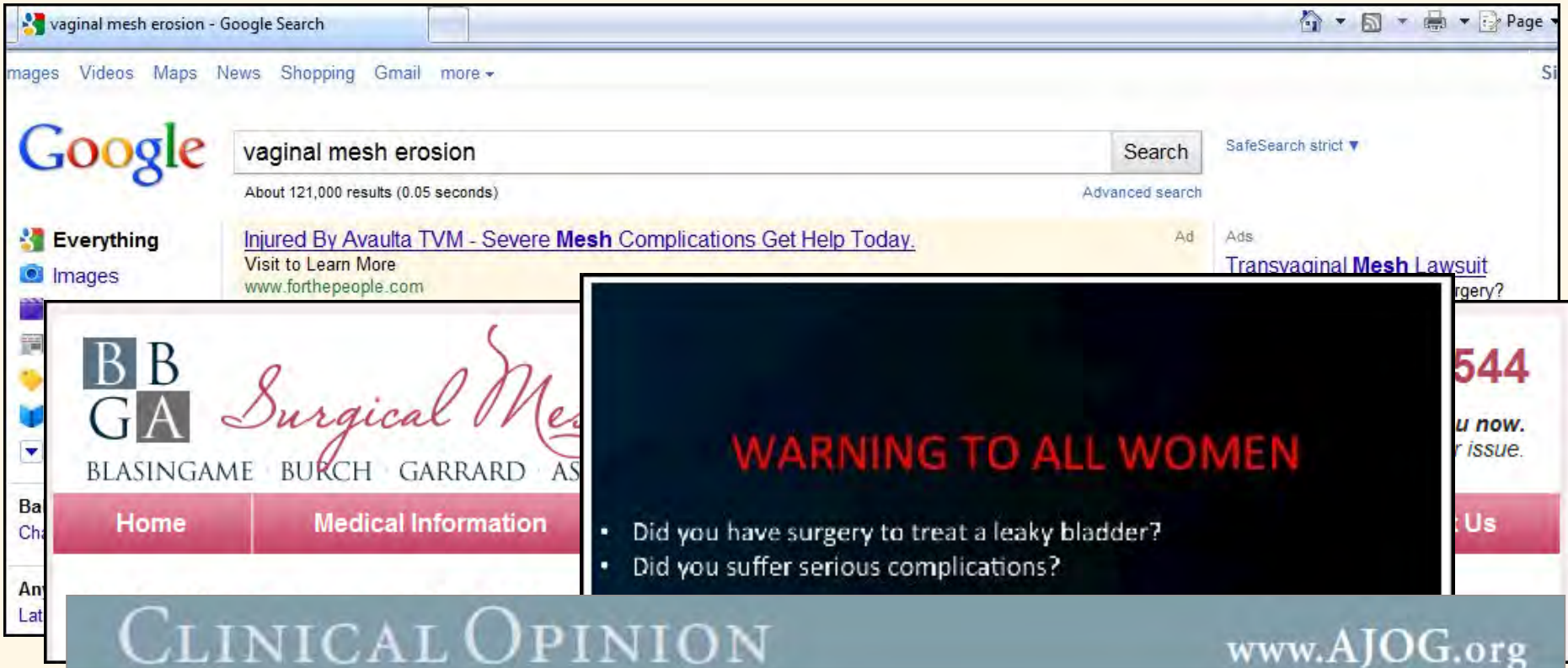


Tommaselli et al. Int Urogynecol J 2015

Success and Complications of Vaginal Mesh POP: Systematic Review

	Apogee™			Prolift™			PIVS			Polypropylene		
	%	SD	95% CI	%	SD	95% CI	%	SD	95% CI	%	SD	95% CI
No. women (*n*)	525			1295			655			178		
Mean follow up (weeks ± SD)	26 ± 15			30 ± 12			46 ± 36			78 ± 47		
Objective success	95.4	3.6	95.1–95.7	86.8	7.3	86.4–87.3	88.2	11.3	87.2–89.1	91.6	4.6	90.9–92.3
Total complication rate	17.6	10.4	16.7–18.5	16.5	11.2	15.9–17.1	12.1	6.1	11.6–12.5	6.9	0.3	6.8–6.9
Mesh erosion	10.7	6.9	10.1–11.3	5.7	4.8	5.5–6.0	7.8	7.1	7.2–8.3	4.6	2.3	4.2–5.0
Dyspareunia	2.7	3.6	2.4–3.0	2.1	2.1	2.0–2.2	1.7	2.8	1.5–1.9	5.5	4.7	4.7–6.3

Feiner et al. BJOG 2009



CLINICAL OPINION www.AJOG.org

UROGYNECOLOGY

Use of vaginal mesh in the face of recent FDA warnings and litigation

Sara J. Mucowski, MD; Catalin Jurnalov, MD; John Y. Phelps, MD, JD, LLM

Tissue Engineering: Individualized Medicine

- Injectable autologous cells
- Tissue engineered grafts for incontinence and prolapse
- Adult stem cells + matrix or scaffold
- Synthetic (polyglycolic acid) or biologic (SIS)

Stem Cell Types

- Embryonic Stem Cells (ESC)
- Amniotic Fluid/Placental Stem Cells (AFPS)
- Induced Pluripotent Stem Cells (IPSC)
- Adult Stem Cells (ASC)
  - Mesenchymal Stem Cells (MSC): most common in urology; harvested from bone marrow, muscle or adipose tissue
  - Urine Derived Stem Cells (USC): easy to obtain, expandable and differentiate into muscle, bone, cartilage and fat

Autologous Muscle Derived Cells for SUI in Women

- Feasibility study
- 38 patients
- Intrasphincteric injection
  - low doses of 1, 2, 4, 8, 16 x 10^6 cells
  - high doses of 32, 64, 128 x 10^6 cells
- Appears safe
- Potential dose response = higher doses

Carr et al. J Urol 2013

Autologous Muscle Derived Cells for SUI in Women

- Safety and efficacy study
- 80 patients
- Intrasphincteric injection
  - doses of 10, 50, 100, 200 x 10^6 cells
- Appears safe
- Potential dose response = higher doses

Peters et al. J Urol 2014

Tissue-engineered Autologous Urethras

- 5 boys, median age 11 years
- Muscle, epithelial cells expanded, seeded onto tubularized polyglycolic acid
- Engineered grafts developed normal-appearing architecture by 3 months
- Tubularized urethras can be engineered and remain remain functional for up to 6 years

Raya-Rivera et al. Lancet 2011

THE LANCET

Volume 384, Issue 9940, 26 July–1 August 2014, Pages 329–336

Articles

Tissue-engineered autologous vaginal organs in patients: a pilot cohort study

Prof Atlántida M Raya-Rivera, MD[a], Prof Diego Esquiliano, MD[a], Prof Reyna Fierro-Pastrana, MD[a], Prof Esther López-Bayghen, PhD[a], Prof Pedro Valencia, MD[a], Prof Ricardo Ordorica-Flores, MD[a], Prof Shay Soker, PhD[b], Prof James J Yoo, PhD[b], Prof Anthony Atala, MD[b,*]

- Vaginal organs engineered from patient's own cells and implanted showed normal structural and functional variables (follow-up ≤8 years)

Conclusions

- There is no ideal material for use in the surgical treatment of female incontinence and POP
- Autologous fascia is probably best available option today but limited in volume with possible harvest site morbidity
- Tissue engineering can provide unlimited autologous tissue with minimal side effects