



CAIRIBU URO-AGING RESEARCH INTEREST GROUP (UroAging RIG)

CAIRIBU URO-AGING KNOWLEDGE EXCHANGES

EXECUTIVE SUMMARY 2/23/2026

URO-AGING RESEARCH INTEREST GROUP

FEAT: KATHLEEN CONNELL, MD

2/23/26 [3-4PM ET]

(2PM CT | 12PM PT)



Goal: Facilitate knowledge exchange and spur collaborations in uro-aging research and adjacent fields

Summary

Histologic Phenotyping of Apical Support Tissue Failure and Regeneration in Pelvic Organ Prolapse

Introduction to Pelvic Organ Prolapse

- **Dr. Connell** provided background on pelvic organ prolapse (POP) and described how the uterosacral ligaments (USL) provide apical support to the vagina and pelvic organs. Loss of apical support is associated with advanced POP. She chose to study the apical support due to ease in obtaining tissue from controls and women with prolapse.
- Risk factors for POP include vaginal delivery, age, parity, BMI, constipation, pulmonary disease, menopause, family history of hernias, family history of prolapse, and diabetes. For recurrent POP, stage at the time of surgery is important.
- To reduce risk of POP, investigators need to understand (1) who is at risk for developing it; (2) who is most likely to fail surgery; (3) what causes the tissues to fail; and (4) the specific POP phenotypes that explain discrepancies in risk stratification, differences in histologic content, and clinical outcomes.
- Previous studies found **inconsistent relationships between USL histology and POP status**. Variations in sample size, race, menopausal status, techniques, and criteria for histology assessment contribute to challenges in understanding POP. To reduce risk for patients, it is important to understand the etiology of POP.
- The OPTIMAL trial demonstrated that recurrent POP occurs in ~60% of women 5 years after USL fixation during hysterectomy. Trial results identified a 10% reoperation rate at five years. This translates to an estimated 35,000 patients needing recurrent surgery for POP per year. But many questions remain.
- **Precision medicine is a promising avenue for addressing POP etiology.** Pan-omic studies and network analyses will allow researchers to identify targets, test them *in vitro* and *in vivo* animal models, and develop treatments.

POP Etiology and Histology

- The precision medicine approach can be paired with a systems approach, the latter of which understands the human body as more than a sum of its parts and explores how organ systems interact.
- Dr. Connell has examined biopsies of USLs, biopsying at the insertion level and cutting ligaments during hysterectomy. **Following preservation and immunohistochemical staining, she classified histologic phenotypes of POP and developed a POP-Histologic Quantification (POP-HQ) tool** to classify these phenotypes and systematically evaluate them.
- Her team noticed prolapse patients exhibit smooth muscle fiber drop out (a loss of smooth muscle cells and smooth muscle fibers), adipose in the middle of the USL, immune cell infiltrates, and increased neointimal hyperplasia.

Principal Components Analysis: POP-HQ Phenotypes and Associated Risk Factors

- Dr. Connell's team identified 3 specific groups differentiated by the presence of (1) increased collagen and aberrant adipose deposition [POP-AC], (2) inflammatory cells and loss of smooth muscle cells [POP-I], and (3) vascular abnormalities [POP-V]. An undifferentiated group, in which USL appeared normal and were undifferentiated from controls when blinded with histopathologist, was also identified.
- Further analysis using UMap dimensionality reduction and Gaussian mixture model clustering helped identify specific phenotypes. For example, **the number of vaginal deliveries correlated directly with adipose content, suggesting damage and fibrosis.**

Immune Cell Infiltration and Extracellular Matrix

- Dr. Connell found the least amount of overlap in patients with prolapse with high immune cell infiltrate vs. controls. Immune cells and extracellular matrix are dependent upon one another in infection, fibrosis, wound repair as well as in homeostasis in general.
- Dr. Connell reviewed **emerging evidence linking immune response to POP**:
 - Increased infiltration of activated neutrophils and activated mast cells in POP USL
 - Immune response and metabolic regulatory pathways in USL and vagina
 - Upregulated immune response genes, complement activation, classical pathway, phagocytosis, and recognition
 - Downregulated genes associated with cellular response to zinc, negative regulation of growth, and apoptotic processes
- Looking more closely, her team saw increased neutrophils, T lymphocytes, macrophages, and some mast cells in the POP-I sub-phenotype.

Elastin and Collagen Turnover

- Two main components of the extracellular matrix are elastin and collagen. Turnover of both contribute to prolapse progression.
 - **Elastin** allows tissue to resume shape after stretching and in the context of the USL, helps apply a counterforce to gravity, which pulls the bowel, uterus, and bladder down. Elastin, which has a 70-year half-life in humans, is synthesized in fetal life and early adulthood and begins to decline in aging. **However, the uterus is an exception**; elastogenesis commences with each new pregnancy, followed by removal of elastin following parturition.
 - In contrast, **collagen** – an essential for wound healing – is synthesized and remodeled through an individual's lifetime; turnover decreases with aging.
- Patients with increased tunica intima with hyperplasia had high elastin content.

Factors Affecting USL and Collagen by Prolapse Risk Factor

- Elastic fiber length in POP-I group was decreased compared to controls, while elastin fiber quantity was increased in POP-I and POP-V sub-phenotypes.
- The quantity in arterial tunica intima was increased in POP-V sub-phenotype. Interestingly, in controls, elastic quantity increased with increasing parity.
- Prolapse is a spectrum, not just discrete stages. Dr. Connell suggested that, **if investigators study women presenting with other issues prior to symptomatic POP, they can follow them post-hysterectomy to study who failed and what their histology looked like prior to surgery.**

Hormone Regulation and Estrogen Receptors

- Estrogen receptor α and β levels vary in prolapse tissues, with studies showing both increased and decreased levels.
- **SNPs associated with POP may influence hormone regulation.**
- Estrogen receptor and androgen receptor expression levels in control USL tissues were similar to those in the POP-A group; POP-I was in between POP-A, control, and POP-V.
- GPR and androgen receptor levels were specifically distinct in the POP-V phenotype versus controls.

Future Directions

- Dr. Connell called out one limitation in POP research, i.e., that human studies require a large number of subjects. A challenge is that controls have other benign conditions.
- **The main takeaway is that histology plays an important role in the precision medicine and systems biology approaches** and allows investigators to study tissues and connect to disease processes and biomechanics.
- Dr. Connell expressed interest in following up with patients after surgery to see whether they failed and seeing what differentiates those who don't fail and creating models to match their phenotype.
- She would like to continue building her infrastructure to scale up and investigate immune pathways and understand regeneration better.

Kathleen A. Connell, MD, is at the University of Colorado Anschutz School of Medicine. She is Professor and Division Chief and holds the William B. Goddard, MD, Endowed Professor in Urogynecology. She is in the Department of Obstetrics and Gynecology and the Divisions of Urogynecology & Pelvic Reconstructive Surgery & Reproductive Sciences. Her primary research goal is to advance scientific research in the field of female pelvic medicine. Her research focuses on the effects of aging and other women's issues on pelvic support, with the ultimate goal of preventing pelvic organ prolapse and developing new treatment options. A link to Dr. Connell's full list of publications is available here: <https://profiles.ucdenver.edu/display/228063>.