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Methods for the Defining Mechanisms of Anterior Vaginal Wall Descent (DEMAND) Study

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Abstract

Introduction and Hypothesis: The protocol and analysis methods for the Defining Mechanisms of Anterior Vaginal Wall Descent (DEMAND) study are presented. DEMAND was designed to identify mechanisms and contributors of prolapse recurrence after two transvaginal apical suspension procedures for uterovaginal prolapse.

Methods: DEMAND is a supplementary cohort study of a clinical trial in which women with uterovaginal prolapse randomized to (1) vaginal hysterectomy with uterosacral ligament suspension or (2) vaginal mesh hysteropexy underwent pelvic magnetic resonance imaging (MRI) at 30-42 months post-surgery. Standardized protocols have been developed to systematize MRI examinations across multiple sites and to improve reliability of MRI measurements. Anatomical failure, based on MRI, is defined as prolapse beyond the hymen. Anatomic measures from co-registered rest, maximal strain, and post-strain rest (recovery) sequences are obtained from the "true midsagittal" plane defined by a 3D pelvic coordinate system. The primary outcome is the mechanism of failure (apical descent versus anterior vaginal wall elongation). Secondary outcomes include displacement of the vaginal apex and perineal body, and elongation of the anterior wall, posterior wall, perimeter, and introitus of the vagina between (1) rest and strain and (2) rest and recovery.

Results: Recruitment and MRI trials of 94 participants were completed by May 2018.

Conclusions: Methods papers which detail studies designed to evaluate anatomic outcomes of prolapse surgeries are few. We describe a systematic, standardized approach to define and

quantitatively assess mechanisms of anatomic failure following prolapse repair. This study will provide a better understanding of how apical prolapse repairs fail anatomically.

BRIEF SUMMARY

The design of DEMAND, a supplementary study that defines mechanisms and contributors of anatomical recurrence after uterovaginal prolapse surgery, is described.

Keywords

Hysteropexy; MRI; Pelvic organ prolapse; Prolapse surgery; Transvaginal mesh; Vaginal hysterectomy

INTRODUCTION:

Pelvic organ prolapse (POP) is a common pelvic floor disorder that adversely affects women's quality of life, including their body image, sexual function, and personal relationships.[1–3] Approximately 12.6% of women will undergo surgery for POP during their lifetime.[4] Native tissue repair (NTR) with concomitant hysterectomy is a common treatment for POP despite its high anatomic failure rate and poor long-term outcomes.[5,6] Of the 300,000 POP surgeries performed annually in the U.S. that use native tissues, up to 15% will fail at 2 years[7] and nearly 12% will require repeat surgery at 5 years[8] due to prolapse recurrence. The primary site of failure is the anterior vaginal wall, with two purported mechanisms–descent of the vaginal apex and anterior vaginal wall elongation associated with fixation of the vaginal apex with sutures (NTR) or mesh (VM). Furthermore, studies suggest that not only does the uterus play a passive role in prolapse, but also that hysterectomy may increase the need for subsequent POP repair.[9]

In response to the high failure rate of NTR, transvaginal mesh (VM) kits have been used to enhance POP repair. In 2010, about one-third of POP surgeries utilized mesh augmentation; 75% of these were performed transvaginally.[10] Though evidence has shown that VM provides high anatomic success in the long-term, its reoperation rate was not superior to traditional NTR due to both mesh-related complications and prolapse recurrence.[11–13] Since 2010, newer VM devices have emerged which utilize lighter, higher porosity polypropylene meshes with the potential for fewer complications. In April 2019, however, the US Food and Drug Administration banned the sale and distribution of VM products, citing that manufacturers failed to demonstrate "reasonable assurance of [long-term] safety and effectiveness" of VM over NTR.[14] Thus, there is a lack of conclusive data on the long-term anatomic benefit of NTR versus VM in the treatment of POP.

To address the knowledge gaps in anatomical failure of POP surgeries prior to the 2019 ban on VM, the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development-sponsored Pelvic Floor Disorders Network (PFDN) designed the Defining Mechanisms of Anterior Vaginal Wall Descent (DEMAND) study. The primary aim of DEMAND is to determine mechanisms and contributors of anterior vaginal wall failure after two procedures for apical repair of uterovaginal prolapse: vaginal hysterectomy with uterosacral ligament suspension (i.e. NTR) versus vaginal mesh hysteropexy (i.e. VM). The

purpose of this paper is to (1) describe the protocol design, (2) illustrate the MRI analysis, and (3) discuss challenges encountered during study development. The overall hypothesis is that following VM, prolapse recurrence in the anterior compartment will occur less commonly than with NTR. Further, we hypothesize that the primary mechanism of anterior wall failure after VM will be elongation of the anterior vaginal wall, whereas after NTR, failures will be caused by both anterior wall elongation and apical descent.

MATERIALS AND METHODS:

Study Design

DEMAND is a planned, supplementary study to the Study of Uterine Prolapse Procedures Randomized (SUPeR) trial[15] that is designed to identify anatomic mechanisms of prolapse recurrence after two transvaginal apical suspension surgeries for uterovaginal prolapse, NTR and VM. This study was conducted across eight clinical sites by the PFDN, a multicenter team of medical researchers and a data coordinating center, sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The study protocol was approved by the University of Pittsburgh Institutional Review Board (IRB # PRO13110579) and IRBs at all other clinical sites. All DEMAND participants provided written informed consent. The participant flow, as well as the data analysis process, is shown in Figure 1.

Study Population

Women treated surgically for uterovaginal prolapse were recruited from the SUPeR trial to undergo pelvic magnetic resonance imaging (MRI) at 30-42 months postoperatively. DEMAND eligibility was determined by the inclusion and exclusion criteria specified in the SUPeR study (see Appendix 1)[15], as well as an MRI contraindication checklist. In addition, women who met SUPeR failure criteria and desired surgical retreatment would be offered participation in DEMAND prior to the 30-42-month window. If consented to participate, these early failures would undergo an MRI prior to their retreatment. The DEMAND cohort consists of women that underwent either vaginal hysterectomy with uterosacral ligament suspension (i.e. NTR) or vaginal mesh hysteropexy (i.e. VM) with the Uphold LITE transvaginal mesh support system (Boston Scientific) as illustrated in Figure 2. The randomization and standardization procedures for these surgeries have been published previously.[15]

Baseline Assessments

For all participants enrolled in DEMAND, the following baseline information was collected within the parent study for comparative analysis of the NTR and VM groups: age, race, ethnicity, marital status, education, medical history, obstetric history, menopausal status, smoking history, and prior prolapse surgery.[15] In addition, preoperative POP-Q measurements and patient-reported outcomes of pelvic floor symptom questionnaires were obtained as part of the parent study.[15].

Imaging Protocol

MRI was performed on a 3T system using a pelvic phased array coil with the participant in the supine position. Before the MRI examination, participants underwent training with clinicians and research staff on how to properly maximally strain. In addition, they were provided with a PowerPoint presentation to reiterate the straining maneuver technique and the importance of achieving maximal strain during the MRI. After participants were positioned on the MRI table, and before placement in the scanner, 10 cc of ultrasound gel was inserted into the vagina to aid visualization of its perimeter. With a speculum, the gel was evenly distributed throughout the vagina and any degree of prolapse was fully reduced.

For the sequences at rest, high resolution, T2-weighted scans of the pelvis were obtained in the axial and coronal planes (repetition time [TR] 2500 ms, echo time [TE] 102 ms, 20x20 cm^2 field of view [FOV], 3-mm slice thickness, 0-mm gap, 180° flip angle, 256x256 matrix). Then, 15 images centered on the vagina were serially obtained in the midsagittal plane for 13.5 s at rest and during strain (TR 900 ms, TE 80 ms, 36x36 cm^2 FOV, 4-mm slice thickness, 1-mm gap, 90° flip angle, 120° refocusing angle, 320x178 matrix). For the strain imaging, participants were told to “bear down” and hold for approximately 20 s once the scanner acquisition began. This process was repeated for a total of three maximal strain trials with a rest period of approximately 15-30 s in between each set. Afterwards, an additional set of high-resolution T2-weighted scans of the pelvis were obtained in the axial plane with the participant at rest, but with prolapse non-reduced, to visualize post-strain recovery (TR 2500 ms, TE 102 ms, 20 × 20 cm^2 FOV, 3-mm slice thickness, 0-mm gap, 180° flip angle, 256x256 matrix).

The rationale for this sequence of images is that the first rest scans establish the initial conditions (i.e. common baseline) for each participant in a reliable, standardized manner. Reducing the prolapse prior to imaging helps straighten the vaginal walls to better delineate the vagina from neighboring anatomic structures. Comparisons between (1) rest and strain and (2) rest and recovery scans will allow quantification of elasticity and recoil of the vaginal tissue, respectively. The recovery scan will allow for measurement of how well the vagina returns to its reduced position following strain; this will provide an assessment of whether supportive structures are still intact and the degree of their mechanical integrity.

All MRI sequences were imported into 3D Sheer (Version 4.10.0, www.slicer.org)[16] to perform image processing and analysis.

Image Co-Registration

A 3D coordinate system based on bony pelvic landmarks identified in the axial rest scans was created using a novel approach developed by Sinex et al.[17] that accounted for differences in patient positioning and alignment in the MRI scanner. First, the x-axis was defined by the line connecting the left and right ischial spines. The midpoint of this axis provided the origin of the coordinate system. To reduce bias, the ischial spine points were identified by two independent examiners. Concordance was achieved when there was < 3 mm difference between point coordinates. Second, the y-axis was defined by the line extending from the origin to the pubic symphysis (PS) such that (1) it was orthogonal to the

x-axis and (2) it intersected at one-third of the inferior-superior length of the PS. This was achieved by generating an ellipse around the PS and calculating one-third of the length of its major axis. The rationale for this axis was that it approximates the level where the levator ani muscles insert into the pubic bone. Third, the z-axis was defined as the cross product of the x- and y-axes. This resulted in a right-handed, orthogonal 3D pelvic coordinate system independent of patient alignment (Figure 3).

For each patient, the MRI sequences were manually co-registered based on the pelvic bones and the 3D pelvic coordinate system. Afterwards, a transformation (i.e. rotation and translation) was applied to the images such that all participants were aligned to a single, global pelvic coordinate system. The y- and-z axes of this global coordinate system are parallel to the horizontal and vertical axes, respectively. The y-z plane defined by this system delineates the “true midsagittal plane” in the rest, maximal strain, and recovery scans used for the imaging analysis.

Imaging Analysis

From the rest, maximal strain, and recovery MRI sequences, the true midsagittal images were selected and imported into 3D Slicer. Of note, when the position of the true mid-sagittal image fell between two collected slices, image interpolation was utilized to generate the true mid-sagittal image. Consistent with SUPeR, anatomic failure was defined as any portion of the vagina protruding past the hymen. To determine this, the vaginal perimeter was outlined and the hymen was defined by a line connecting the anterior and posterior hymenal remnants. Vaginal protrusion beyond the hymenal line signified failure by MRI criteria. The site of failure (e.g. anterior, posterior, or apical vaginal compartment) was also identified.

For MRI failures, the mechanism of anterior prolapse recurrence was classified as either anterior vaginal wall elongation or apical descent. Anterior vaginal wall elongation was defined as a >20% increase in the anterior vaginal wall length from rest to strain; this threshold takes into account objective and subjective measurement variability. Apical descent was defined as descent of the vaginal apex in the absence of anterior vaginal wall elongation from rest to strain. Prolapse recurrence associated with descent of the posterior vaginal wall will be analyzed separately.

To determine vaginal length, digital fiducial markers were placed along the vagina to create a 3D curve using an interpolation algorithm. The location of the vaginal apex was also marked in the image. Using the vaginal apex and hymenal remnants to demarcate the anterior and posterior portion of the vagina, the lengths of the anterior wall, posterior wall, and vaginal perimeter were calculated. The distance between the anterior and posterior hymenal remnants were used to find the length of the vaginal introitus. The posterior wall length and introitus size approximate the total vaginal length and genital hiatus POP-Q measures, respectively. The point coordinates of the posterior hymenal remnant were used to estimate the position of the perineal body. Finally, the displacement vectors (i.e. descent) of the vaginal apex and perineal body, and the change in length of the anterior wall, posterior wall, and perimeter of the vagina from (1) rest to strain and (2) rest to recovery were calculated (Figure 4).

Vaginal descent, as well as orientation and position, were visualized by finding the proximal (upper) and distal (lower) axes of the vagina in the true midsagittal plane with respect to the 3D pelvic coordinate system (Figure 5). To determine the vaginal axes, the coordinates of the anterior and posterior hymenal remnants, halfway points of the anterior and posterior vaginal walls, and vaginal apex were identified along the vaginal contour. The vaginal apex and the midpoints between (1) the hymenal remnants and (2) halfway points were used to delineate the upper and lower axes of the vagina. The angles of these axes from the horizontal axis of the pelvic coordinate system, and the angle between the two vaginal axes, were calculated. To compare vaginal measures across patients, the data was normalized for patient size. The MRI analysis will be performed by two observers.

Planned Outcomes

For this study, the primary outcome was the mechanism of failure: (1) apical descent or (2) anterior vaginal wall elongation. In addition, the rate and leading edge of prolapse (e.g. anterior, apical, posterior compartment(s)) were noted. Secondary outcomes included the following: displacement of the vaginal apex and perineal body, and change in length of the anterior vaginal wall, posterior vaginal wall, and vaginal introitus between (1) rest and strain and (2) rest and recovery.

Other clinically relevant outcomes investigated in this study were group differences in baseline characteristics between (1) NTR and VM and (2) MRI successes and failures; agreement of MRI- with SUPeR criteria-based[15] in failure outcomes; and concordance between MRI and POP-Q measures (i.e. total vaginal length, genital hiatus).

Statistical Approach

Because DEMAND was designed primarily as a descriptive study, formal sample size calculations were not conducted. However, based on a preliminary inter- and intraobserver reliability study,[17,18] it was estimated that 40 participants in each surgical repair group would provide approximately 80% power to detect a moderate effect size between the two treatments.

The primary outcome, as well as the frequency and site of failure, between NTR and VM will be assessed using Fisher’s exact tests. Extensions of linear models will be used to jointly model the amount of anterior wall descent resulting from descent of the apex and from elongation of the anterior vaginal wall, and differences between treatment groups will be evaluated. Secondary outcome measures will be compared between (1) NTR and VM and (2) MRI-defined successes and failures using Wilcoxon Rank-Sum tests. Similarly, Fisher’s exact tests and Wilcoxon Rank-Sum tests will be performed to evaluate differences in baseline demographics and clinical characteristics with respect to (1) the type of surgical repair and (2) MRI outcome. Agreement of failure outcomes between MRI and SUPeR criteria will be determined using the kappa statistic.

Correlations in measurements of the total vaginal length and genital hiatus between MRI and POP-Q will be assessed using Pearson correlation.

RESULTS:

Study recruitment and MRI trials were completed in May 2018. A total of 94 out of the 183 SUPeR participants offered enrollment have enrolled in DEMAND. Of the 94 DEMAND participants, 89 were eligible for MRI analysis with 44 in the NTR arm and 45 in the VM arm. Five of the 94 participants were excluded from MRI analysis due to incomplete MRI (N = 1) and failure to image the entire vagina during strain (N = 4).

DISCUSSION:

There were a few challenges encountered during the design of DEMAND. Approaches to address these challenges, as well as the significance of DEMAND are discussed below.

Challenges in Designing DEMAND

Capturing Failure—We aimed to capture failure as close to the SUPeR primary endpoint at three years post-surgery as possible, but within a reasonable time window in order to maximize enrollment. Therefore, we imaged women 30-42 months after surgery. Women with prolapse recurrence desiring surgical retreatment before this time point were imaged prior to their second surgery. Women with recurrence who chose to be managed with a pessary were encouraged to wait until 30-42 months for imaging. Only half of SUPeR patients agreed to participate in DEMAND. Therefore, our population does not represent the full randomized population of SUPeR. Importantly, surgical failure rates increase with time. Thus, while 36 months is reasonable to capture failure, it is likely that more women will experience prolapse recurrence over time.

Achieving Consistency in Performing the MRI Over Multiple Sites—The multi-center design of this study introduced complexity in coordinating and maintaining consistency in the MRI evaluations conducted across multiple clinical sites. To ensure that all sites performed the MRI trials consistently, an MRI checklist was created that was completed by the MRI technicians. During imaging, the technologists were asked a series of yes or no questions. If the technologists failed to complete a step, they were required to repeat that portion of the scan. Following the dynamic MRI sequences, the technicians were instructed to ask the patient if she felt that she achieved maximal strain during the procedure. If the patient replied “no”, then the dynamic portion was repeated. At the end of the study, technologists were asked whether they thought the study was adequate based on a Likert scale from “not likely” to “very likely”. Each site had a designated radiologist experienced in performing dynamic MRI who participated in a webinar reviewing the technical aspects of MRI acquisition. This webinar was available on the PFDN website for radiologists to refer to when training MRI technologists at their site, or prior to a study. The first five scans at each site were reviewed by a study radiologist (ML), urogynecologist (PM), and bioengineer (SA) to ensure that the scans were capturing study endpoints properly.

Capturing Maximal Strain During Dynamic MRI—An important limitation of this study is that the imaging is performed in the supine position and therefore, maximal descent is dependent on patient effort and proper straining technique. To address this, we have repeatedly trained patients on performance of the strain maneuver during their follow-up

visits, instructed them in a PowerPoint presentation which they were allowed to view multiple times prior to their MRI, and asked them after their MRI procedure if they thought they had achieved maximal strain. If they believed that they had not, they were allowed to undergo an additional maximal strain MRI sequence. Tumbarello showed that three repeated strain maneuvers resulted in a greater pelvic organ descent than one or two strain attempts.[19] While it is not certain that all women in the study achieved maximal strain, we believe that these methods increased the likelihood that it was accomplished. Finally, Swenson found that only 0.8 N (<0.2 lb.) of traction force was needed to reproduce maximal strain observed on MRI; this suggests that most women achieve maximal strain with reasonable effort.[20]

Establishing a 3D Pelvic Coordinate System—The approach to define the 3D pelvic coordinate system minimizes user input by limiting it to identifying the points of the ischial spines that define the x-axis. The source of error is therefore the quality of the images (e.g. resolution, signal intensity, slice thickness, slice spacing) that impacts the ability to reliably identify the ischial spines. Thus, intra- and inter- observer reliability depended on the specific image sequence used with this approach.

To minimize the error in the ischial spine coordinates, web-based technologies were created to facilitate and standardize the annotation process. For each MRI sequence, a single slice was shown as a clickable background image on a web page. JavaScript technologies were used to create an online annotation tool. When an annotator selected a point on the image, the image coordinates were captured. These coordinates were then converted to actual measurements using meta-data from the DICOM file. Once the annotator selected the left and right ischial spine points, the measurements were submitted back to a server and stored in a database.

After both annotators completed their measurements, concordance was determined by calculating the Euclidean distance of corresponding points between both annotators. If the distance between corresponding points was less than or equal to 3 mm, concordance is reached; if not, both annotators repeated the process, with up to three attempts allowed. If there was no agreement after these attempts, the annotators reviewed the images in consensus. When concordance was achieved, email notifications were sent, and the image sequences were made available for download on the website. For each patient dataset that was uploaded, a ZIP file was created that contained the DICOM images, and the ischial spine coordinates given by both annotators were stored in an Excel spreadsheet.

Defining Descent Using Finite Element Modeling—The original protocol for DEMAND included the use of finite element analysis of MRI derived 3D computational models to measure changes in vaginal position, orientation, and length as a method to quantitatively compare mechanisms of anterior vaginal wall descent. Such an analysis involves mapping 3D image volumes of the vagina from rest to strain using a Hyperelastic Warping algorithm in order to drive the finite element model. However, deformations of the vagina were too large and computationally intensive for feasibility of this approach, particularly in women with prolapse recurrence, who comprised a significant portion of each group. Thus, we developed an alternative, 2D analysis framework that was computationally efficient and achieved comparable results (~95%) in real-time.

Importance of the DEMAND Study

To date, researchers have been unable to define the mechanisms of failure following POP surgery. Traditionally, POP-Q and clinical evaluation have been used to investigate the outcomes of POP repair.[21,22] However, the information obtained from this approach has limited use in identifying the anatomic causes of prolapse recurrence. Increasing evidence suggests that anatomical failure is a biomechanical process. Thus, a biomechanical understanding of how and why operations fail is necessary to improve the treatment and prevention of POP and its recurrence, respectively.[23]

Bioimaging methods such as MRI are useful for quantifying anatomic factors related to POP in situations when conventional tools like POP-Q are unable to do so as effectively. Recently, a few studies used MRI to determine the efficacy of POP repairs.[24–26] These analyses often used 2D midsagittal images along with (1) reference lines based on the bony and soft tissue landmarks of the pelvis and (2) POP-Q to quantify anatomical measures and identify different types of recurrent prolapse after POP surgery. However, differences in failure criteria, poor reliability of defining the reference lines due to variations in patient alignment, and limitations in assessing internal anatomy with POP-Q have made it difficult to reach consensus on mechanisms of failure.

To address these issues, DEMAND was designed to incorporate a standardized approach to evaluate and compare anatomical outcomes of POP procedures using MRI with a 3D pelvic reference system, clinical examination, and questionnaires. The combination of these methods will augment the assessment of surgical outcomes, as well as better identify the different mechanisms and correlates of anatomical failure observed in prolapse recurrences. The findings of DEMAND will provide preliminary knowledge of the anatomic mechanisms and contributors involved in recurrent prolapse after apical suspension procedures. The resulting information will be used toward developing a new assessment method that not only evaluates anatomic outcomes of POP repair, but may also aid surgeons in counseling and treatment planning for patients with POP and could lead to future treatments and studies addressing prevention of anatomic failure.

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APPENDIX 1:

The following is a direct excerpt of a supplementary file from the parent study (SUPeR Trial)[15] that detailed its inclusion and exclusion criteria which was adopted by the DEMAND study:

Inclusion Criteria

1. Women aged 21 or older who have completed child -bearing
2. Prolapse beyond the hymen (defined as Ba, Bp, or C > 0 cm)
3. Uterine descent into at least the lower half of the vagina (defined as point C> -TVL/2))
4. Bothersome bulge symptoms as indicated on question 3 of the PFDI-20 form relating to 'sensation of bulging' or 'something falling out'
5. Desires vaginal surgical treatment for uterovaginal prolapse
6. Available for up to 60-month follow-up
7. Amenorrhea for the past 12 months from either menopause or endometrial ablation
8. Not pregnant, not at risk for pregnancy or agree to contraception if at risk for pregnancy (only applicable to the rare endometrial ablation patient)
9. Eligible for no cervical cancer screening for at least 3 years

Exclusion Criteria

1. Previous synthetic material (placed vaginally or abdominally) to augment POP repair
2. Known previous uterosacral or sacrospinous uterine suspension
3. Known adverse reaction to synthetic mesh or biological grafts; these complications include but are not limited to erosion, fistula, or abscess
4. Chronic pelvic pain

5. Pelvic radiation
6. Cervical elongation- defined as an expectation that the C point would be Stage 2 or greater postoperatively if a hysteropexy was performed. (Note: cervical shortening or trachelectomy is 18 not an allowed intraoperative procedure within the hysteropexy treatment group).
7. Women at increased risk of cervical dysplasia requiring cervical cancer screening more often than every 3 years (e.g. HIV+ status, immunosuppression because of transplant related medications, Diethylstilbestrol (DES) exposure in utero, or previous treatment for cervical intraepithelial neoplasia (CIN)2, CIN3, or cancer)
8. Uterine abnormalities (symptomatic uterine fibroids, polyps, endometrial hyperplasia, endometrial cancer, or any uterine disease that precluded prolapse repair with uterine preservation in the opinion of the surgeon
9. Indication for ovarian removal (adnexal mass, BRCA 1/2 positivity, family history of ovarian cancer)
10. Current condition of amenorrhea caused by exogenous sex steroids or hypothalamic conditions.

ABBREVIATIONS:

DEMAND	Defining Mechanisms of Anterior Vaginal Wall Descent
MRI	Magnetic Resonance Imaging
POP	Pelvic Organ Prolapse
NTR	Native Tissue Repair
VM	Transvaginal Mesh
POP-Q	Pelvic Organ Prolapse Quantification
PFDN	Pelvic Floor Disorders Network
SUPeR	Study of Uterine Prolapse Procedures Randomized

REFERENCES:

1. Digesu GA, Chaliha C, Salvatore S, Hutchings A, Khullar V. The relationship of vaginal prolapse severity tosymptoms and quality of life. BJOG An Int J Obstet Gynaecol. 2005;112(7):971–976. doi:10.1111/j.1471-0528.2005.00568.x
2. Zielinski R, Miller J, Low LK, Sampselle C, Delancey JOL. The relationship between pelvic organ prolapse, genital body image, and sexual health. Neurourol Urodyn. 2012;31(7):1145–1148. doi:10.1002/nau.22205 [PubMed: 22473490]
3. Handa VL, Cundiff G, Chang HH, Helzlsouer KJ. Female sexual function and pelvic floor disorders. Obstet Gynecol. 2008; 111(5):1045–1052. doi:10.1097/AOG.0b013e31816bbe85 [PubMed: 18448734]
4. Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. Obstet Gynecol. 2014;123(6):1201–1206. doi:10.1097/AOG.0000000000000286 [PubMed: 24807341]

5. Eilber KS, Alperin M, Khan A, et al. Outcomes of vaginal prolapse surgery among female medicare beneficiaries: the role of apical support. Obstet Gynecol. 2013;122(5):981–987. doi:10.1097/AOG.0b013e3182a8a5e4 [PubMed: 24104778]
6. Davila GW, Baessler K, Cosson M, Cardozo L. Selection of patients in whom vaginal graft use may be appropriate: Consensus of the 2nd IUGA grafts roundtable: Optimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery. Int Urogynecol J. 2012;23(SUPPL. 1). doi:10.1007/s00192-012-1677-3
7. Barber MD, Brubaker L, Burgio KL, et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: The OPTIMAL randomized trial. JAMA - J Am Med Assoc. 2014;311(10):1023–1034. doi:10.1001/jama.2014.1719
8. Jelovsek JE, Barber MD, Norton P, et al. Effect of uterosacral ligament suspension vs sacrospinous ligament fixation with or without perioperative behavioral therapy for pelvic organ vaginal prolapse on surgical outcomes and prolapse symptoms at 5 years in the OPTIMAL randomized clinical trial. JAMA - J Am Med Assoc. 2018;319(15):1554–1565. doi:10.1001/jama.2018.2827
9. Lykke R, Blaakear J, Ottesen B, Gimbel H. The indication for hysterectomy as a risk factor for subsequent pelvic organ prolapse repair. Int Urogynecol J. 2015;26(11):1661–1665. doi:10.1007/s00192-015-2757-y [PubMed: 26049977]
10. Jonsson Funk M, Edenfield AL, Pate V, Visco AG, Weidner AC, Wu JM. Trends in use of surgical mesh for pelvic organ prolapse. Am J Obstet Gynecol. 2013;208(1):79.e1–79.e7. doi:10.1016/j.ajog.2012.11.008 [PubMed: 23159692]
11. Maher CM, Feiner B, Baessler K, Glazener CMA. Surgical management of pelvic organ prolapse in women: The updated summary version Cochrane review. In: International Urogynecology Journal. Vol 22. Springer London; 2011:1445–1457. doi:10.1007/s00192-011-1542-9 [PubMed: 21927941]
12. Feiner B, Jelovsek JE, Maher C. Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: A systematic review. BJOG An Int J Obstet Gynaecol. 2009;116(1):15–24. doi:10.1111/j.1471-0528.2008.02023.x
13. Diwadkar GB, Barber MD, Feiner B, et al. Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. Am J Obstet Gynecol. 2011;205(3):230.e1–230.e5. doi:10.1016/j.ajog.2011.03.046 [PubMed: 21600549]
14. FDA takes action to protect women's health, orders manufacturers of surgical mesh intended for transvaginal repair of pelvic organ prolapse to stop selling all devices | FDA. https://www.fda.gov/news-events/press-announcements/fda-takes-action-protect-womens-health-orders-manufacturers-surgical-mesh-intended-transvaginal. Accessed January 14, 2020.
15. Nager CW, Visco AG, Richter FIE, et al. Effect of vaginal mesh hysteropexy vs vaginal hysterectomy with uterosacral ligament suspension on treatment failure in women with uterovaginal prolapse: A randomized clinical trial. JAMA - J Am Med Assoc. 2019;322(11):1054–1065. doi:10.1001/jama.2019.12812
16. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Sheer as an image computing platform for the Quantitative Imaging Network. Magn Resort Imaging. 2012;30(9): 1323–1341. doi:10.1016/j.mri.2012.05.001
17. Easley DC, Menon PG, Abramowitch SD, Moalli PA. Inter-observer variability of vaginal wall segmentation from MRI: A statistical shape analysis approach. In: AS ME International Mechanical Engineering Congress and Exposition, Proceedings (IMECE). Vol 3-2015. American Society of Mechanical Engineers (ASME); 2015. doi:10.1115/IMECE2015-53499
18. Floyte L, Brubaker L, Fielding JR, et al. Measurements from image-based three dimensional pelvic floor reconstruction: A study of inter- and intraobserver reliability. J Magn Reson Imaging. 2009;30(2):344–350. doi:10.1002/jmri.21847 [PubMed: 19629987]
19. Tumbarello JA, Flsu Y, Lewicky-Gaupp C, Rohrer S, DeLancey JOL. Do repetitive Valsalva maneuvers change maximum prolapse on dynamic MRI? Int Urogynecol J. 2010;21(10): 1247–1251. doi: 10.1007/S00192-010-1178-1 [PubMed: 20544342]
20. Swenson CW, Luo J, Chen L, Ashton-Miller JA, DeLancey JOL. Traction force needed to reproduce physiologically observed uterine movement: technique development, feasibility assessment, and preliminary findings. Int Urogynecol J. 2016;27(8):1227–1234. doi:10.1007/s00192-016-2980-1 [PubMed: 26922179]

21. Kowalski JT, Mehr A, Cohen E, Bradley CS. Systematic review of definitions for success in pelvic organ prolapse surgery. Int Urogynecol J. 2018;29(11):1697–1704. doi:10.1007/s00192-018-3755-7 [PubMed: 30143852]

22. Meister MRL, Sutcliffe S, Lowder JL. Definitions of apical vaginal support loss: a systematic review. In: American Journal of Obstetrics and Gynecology. Vol 216. Mosby Inc.; 2017:232.e1–232.e14. doi:10.1016/j.ajog.2016.09.078 [PubMed: 27640944]

23. The JOD hidden epidemic of pelvic floor dysfunction: achievable goals for improved prevention and treatment. Am J Obstet Gynecol. 2005;192(5):1488–1495. doi:10.1016/j.ajog.2004.11.014 [PubMed: 15902147]

24. Kashihara H, Emmanuelli V, Poncelet E, et al. Comparison of dynamic MRI vaginal anatomical changes after vaginal mesh surgery and laparoscopic sacropexy. Gynecol Surg. 2014;11(4):249–256. doi:10.1007/s10397-014-0864-2

25. Kasturi S, Lowman J, Kelvin FM, Akisik F, Terry C, Hale DS. Pelvic magnetic resonance imaging for assessment of the efficacy of the Prolift system for pelvic organ prolapse. In: American Journal of Obstetrics and Gynecology. Vol 203. Mosby Inc.; 2010:504.e1–504.e5. doi:10.1016/j.ajog.2010.06.034 [PubMed: 20691416]

26. Arenholt LTS, Pedersen BG, Glavind K, Greisen S, Bek KM, Glavind-Kristensen M. Prospective evaluation of paravaginal defect repair with and without apical suspension: a 6-month postoperative follow-up with MRI, clinical examination, and questionnaires. Int Urogynecol J. 2019;30(10):1725–1733. doi:10.1007/s00192-018-3807-z [PubMed: 30506182]

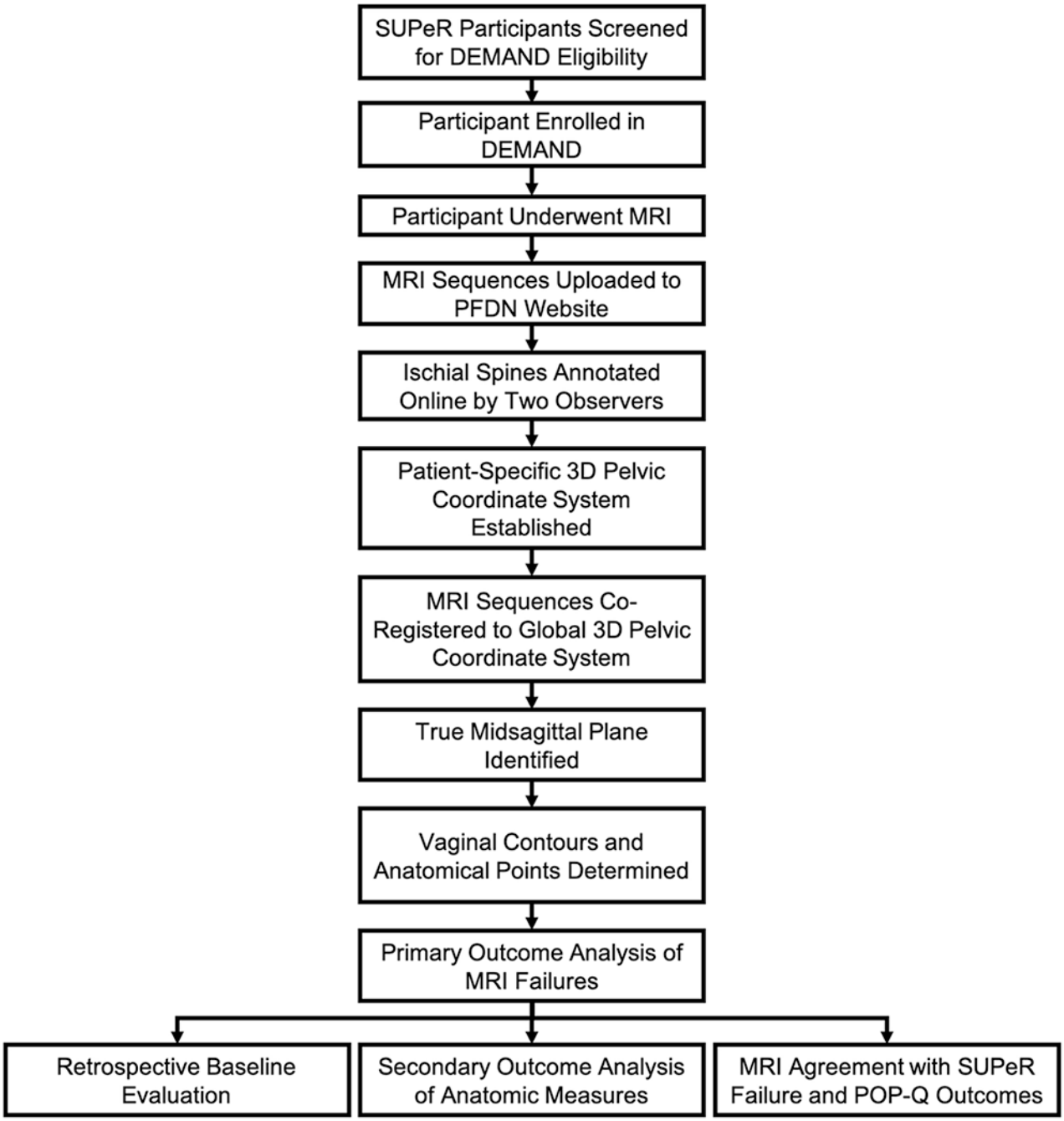

Figure 1.
Diagram of participant flow and data analysis.

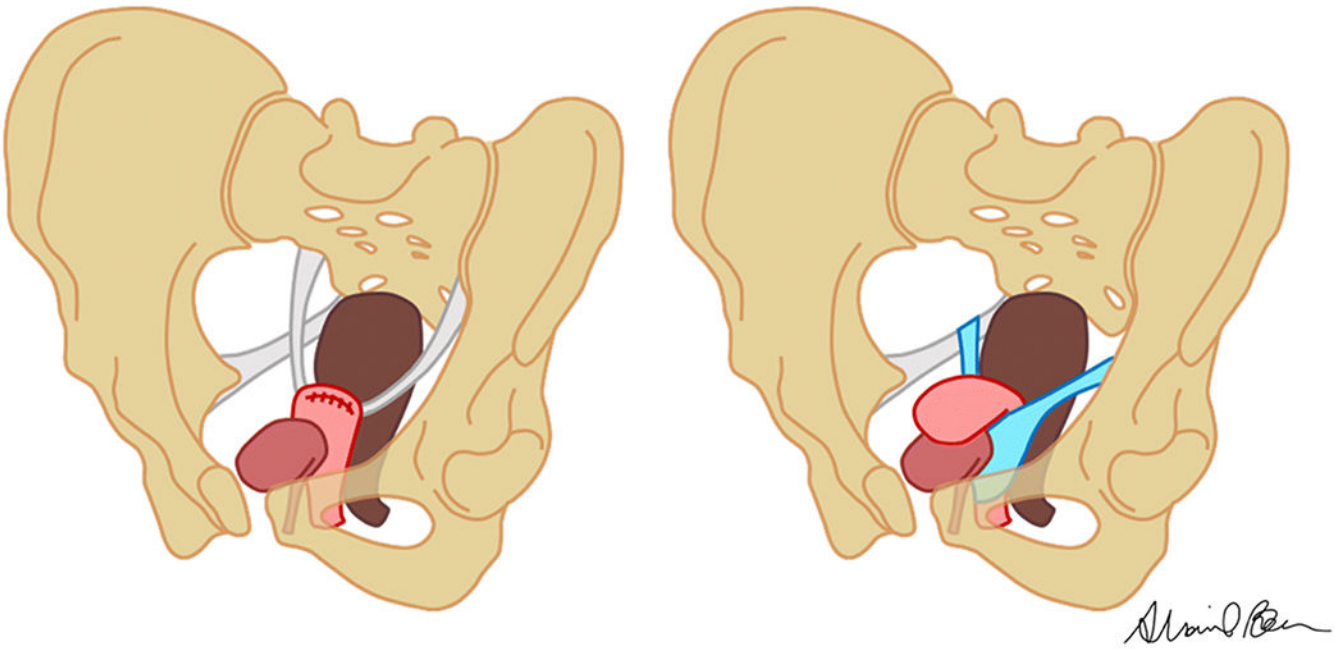

Figure 2.

Two transvaginal surgical procedures compared in DEMAND. Left: vaginal hysterectomy with uterosacral ligament suspension. Right: vaginal mesh (sacrospinous) hysteropexy with Uphold Lite device.

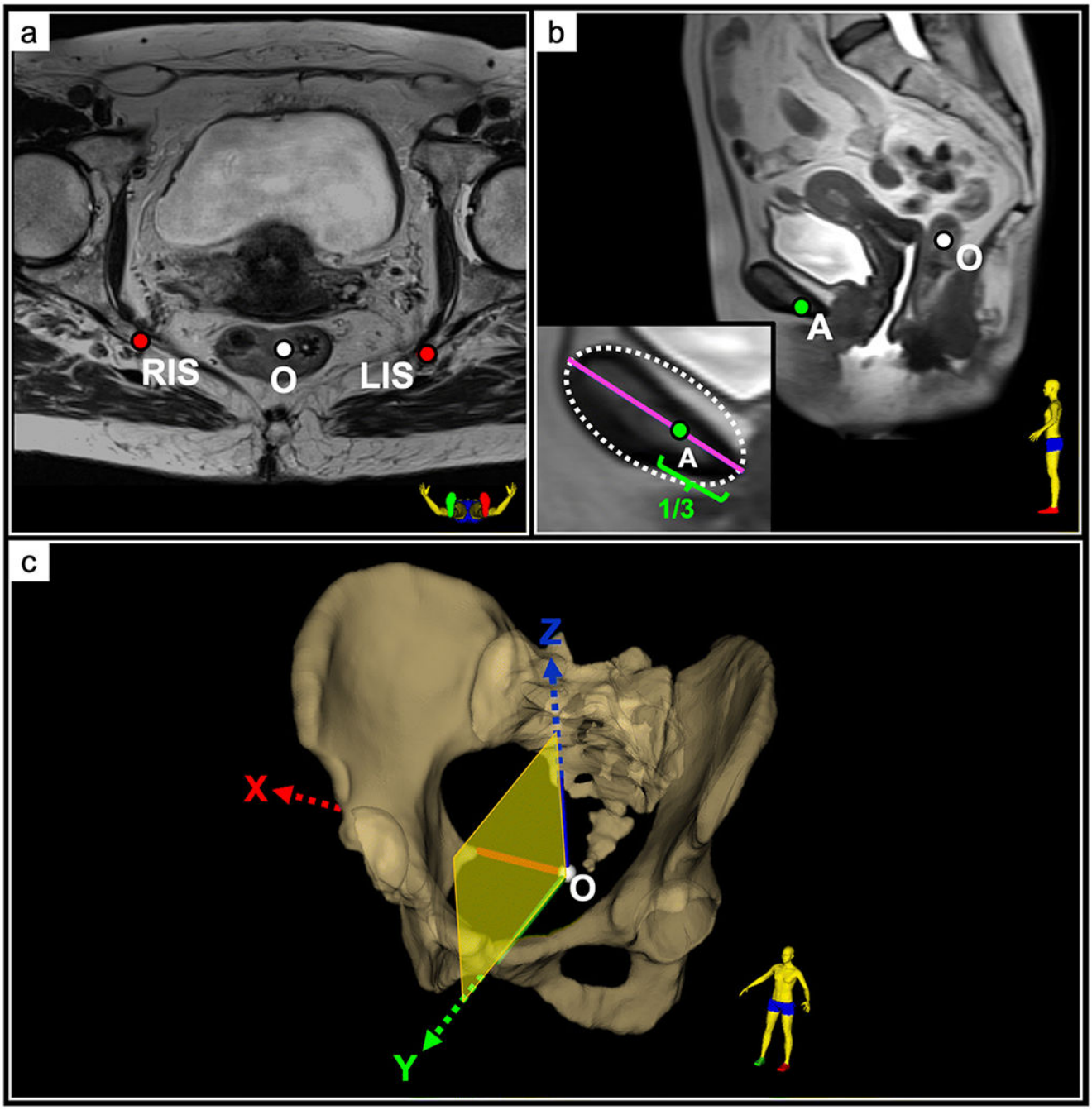

Figure 3.

Establishment of the 3D pelvic coordinate system: (a) axial T2-weighted MRI scan showing right ischial spine (RIS), left ischial spine (LIS), and origin (O) points that define the x-axis; (b) midsagittal MRI scan showing points A, determined by one-third the major axis (pink line) of the pubic symphysis ellipse (dotted white line), and O that delineate the y-axis; (c) 3D view illustrating coordinate system with respect to the bony pelvis. The “true midsagittal plane” (yellow region) is given by the y-z plane of the pelvic coordinate system.

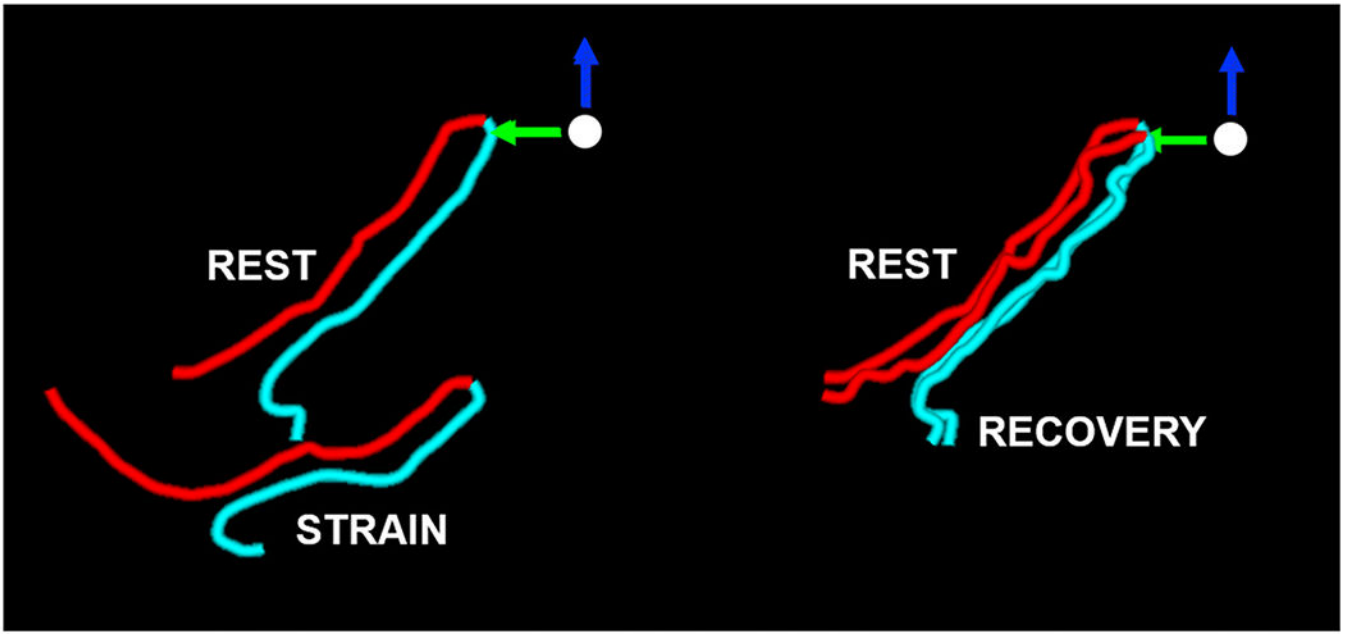

Figure 4.

Comparisons in vaginal contours and anatomic measures between rest vs strain (left) and rest vs recovery (right) with respect to the Y (green) and Z axes (blue) of the 3D pelvic coordinate system. Outlines of the anterior vaginal wall (red contour) and posterior vaginal wall (cyan contour) are displayed.

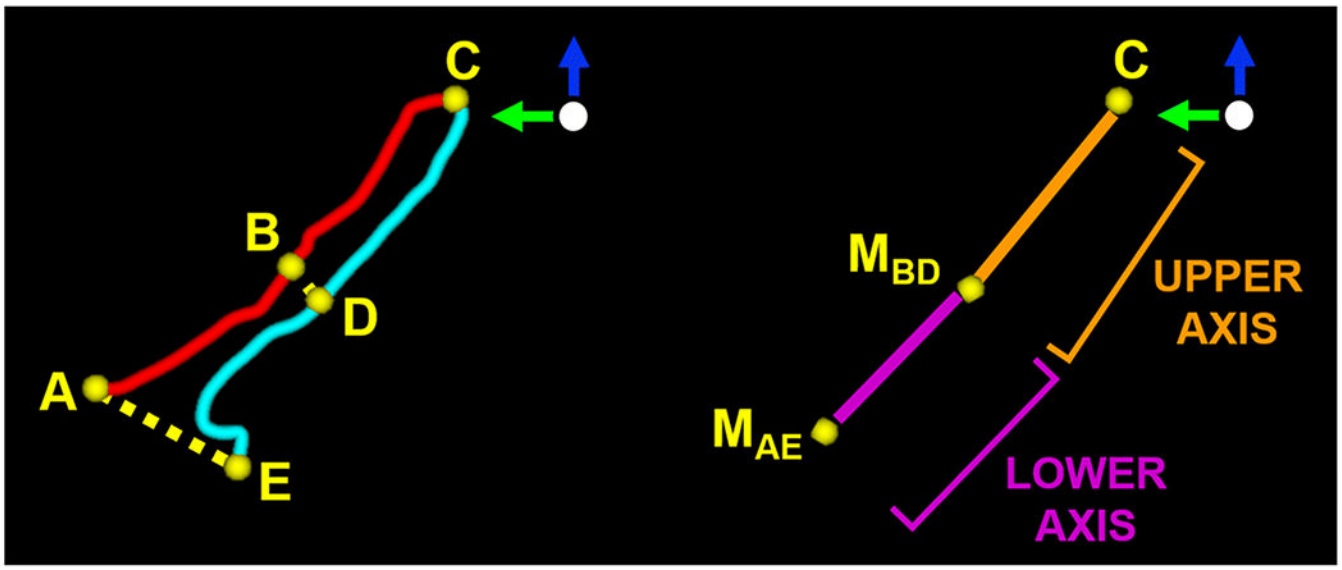

Figure 5.

Visualization of the vaginal position and orientation with respect to the Y (green) and Z axes (blue) of the 3D pelvic coordinate system. Left: anterior hymenal remnant (point A), halfway point of the anterior vaginal wall (point B), vaginal apex (point C), halfway point of the posterior vaginal wall (point D), and posterior hymenal remnant (point E) are identified along the vaginal contour. The distance between the hymenal remnants (dotted line AE) and halfway points (dotted line BD) are also displayed. Right: vaginal apex (point C) and midpoints of the i) hymenal remnants (point M_{AE}) and ii) halfway marks (point M_{BD}) delineate the upper axis (orange line) and lower axis (purple line) of the vagina.