A randomized trial comparing perioperative pelvic **FLO**or physical therapy to current standard of care in transgender **W**omen undergoing vaginoplasty for gend**ER** affirmation

The FLOWER Trial

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BACKGROUND

In the natal male, the pelvic floor is comprised of bulbospongiosus, ischiocavernosus, deep transverse perineal, superficial transverse perineal, pubococcygeus, and obturator internus muscles; as well as the perineal body, external anal sphincter, anococcygeal ligament, coccyx, ischial tuberosities and the sacrotuberous ligament. Pelvic floor dysfunction, including urinary symptoms, bowel symptoms, sexual dysfunction and pelvic pain is often thought of a "female-centric" condition, and pelvic floor physical therapy (PFPT) is often used as first or second line therapy to treat many of these conditions in natal women. However, natal men also experience pelvic floor symptoms and while the literature is not as abundant in this patient population, there are data to support the use of physical therapy as primary and adjunctive therapy for many conditions in men.

In a prospective study by Masterson et al. (1) the authors evaluated 14 men with chronic pelvic pain syndrome who underwent a comprehensive PFPT program. Treatment included manual therapy (internal and external) of the pelvic floor and abdominal musculature to facilitate relaxation of muscles; therapeutic exercises to promote range of motion, improve mobility/flexibility and strengthen weak muscles; biofeedback to facilitate strengthening and relaxation of pelvic floor musculature; and neuromodulation for pelvic floor muscle relaxation and pain relief. A robust treatment response was found in 50% of patients while 20% reported a moderate response and 30% did not have a meaningful change. Longer duration of therapy predicted treatment response.

In a review of the literature by Cohen et al (2), the authors found that there was evidence supporting the association between the male pelvic floor and erectile dysfunction, ejaculatory/orgasmic dysfunction, and chronic prostatitis/chronic pelvic pain syndrome, respectively. The authors concluded that pelvic floor physical therapy is a necessary tool for the treatment of male

sexual dysfunction and pelvic pain. In a systematic review, PFPT was also been shown to be beneficial for the treatment of urinary incontinence in men who had undergone prostatectomy for prostate cancer (3).

Transgender women are individuals who were assigned male at birth (are biologically male), but identify as female. Vaginoplasty surgery is a gender- affirming genital surgery for transgender women seeking surgical transition. The goal of vaginoplasty is to create a natural-appearing vulva with a sensate clitoris, a female urethra, and in those patients who desire it, a vaginal canal. In constructing the neovaginal canal, a space is created between the rectum and the bladder, which requires dissection through the pelvic floor musculature. This dissection divides parts of the levator ani complex, which may affect pelvic floor function. As such, PFPT may have an important role in the perioperative management of transgender women undergoing vaginoplasty.

The only study published to date examining the effect of PFPT on all patients undergoing vaginoplasty was recently published by Jiang et al (4). In this retrospective analysis, the authors aimed to describe the incidence of pelvic floor dysfunction in transgender women undergoing gender-affirming vaginoplasty as well as to describe outcomes from their postoperative PFPT program. Over a two-year period, 77 patients were referred to PFPT postoperatively following vaginoplasty and all patients attended at least one session. Preoperatively, PFPT assessment identified an incidence of 42% for pelvic floor dysfunction and 37% for bowel dysfunction. Of those patients found to have dysfunction preoperatively, resolution after the first postoperative pelvic floor PT visit was 69% for pelvic floor dysfunction and 73% for bowel dysfunction. In addition, the authors found that the incidence of postoperative pelvic floor dysfunction was even lower in patients who attended pre- and postoperative PFPT versus postoperative PFPT alone.

There is further evidence that patients undergoing vaginoplasty surgery may have preoperative pelvic floor dysfunction symptoms that should be addressed before and after surgery. In a retrospective study by Manrique et al (5), patients scheduled to undergo male-to-female vaginoplasty were evaluated by a physical therapist for pelvic floor dysfunction and patients with pelvic floor symptoms underwent pre- and postoperative PFPT. The authors found that of the 40 patients evaluated, 31 (77.5%) were found to be symptomatic and that physical therapy significantly reduced severity of symptoms and its impact on daily living following surgery.

Currently, perioperative PFPT is not standard of care for all patients who undergo vaginoplasty surgery. While some practices have implemented these new programs, and the above data exist on outcomes associated with perioperative PFPT in transgender women undergoing vaginoplasty, no study has compared implementation of perioperative PFPT to routine care (no perioperative PFPT). Therefore, the primary objective of this study to compare the effectiveness of postoperative PFPT compared to no PFPT in transgender women undergoing vaginoplasty surgery for gender affirmation. Secondary objectives of the study are 1) to describe the incidence of preoperative pelvic floor dysfunction in transgender women undergoing PFPT and 2) to compare the

effectiveness of postoperative PFPT alone to pre- and postoperative PFPT in these patients.

STUDY METHODS

Study Design: Randomized double-blind study

Both subjects and the surgeon performing the surgery as well as the personnel administering questionnaires to patients postoperatively will be blind to randomization

Primary Aim

To compare the effectiveness of postoperative PFPT compared to no PFPT in transgender women undergoing vaginoplasty.

> *Primary Outcome: Patient reported ease of dilation at 12 weeks (VAS 0-10)*
>
> *Secondary Outcome: Severity of pelvic floor dysfunction at 12 weeks (questionnaires)*

Secondary Aims

To describe the incidence of preoperative pelvic floor dysfunction in transgender women undergoing PFPT.

To compare the effectiveness of postoperative PFPT alone to pre- and postoperative PFPT in these patients.

> *Primary Outcome: Patient reported ease of dilation at 12 weeks (VAS 0-10)*
>
> *Secondary Outcome: Severity of pelvic floor dysfunction at 12 weeks (questionnaires)*

Study Population: All transgender women undergoing vaginoplasty surgery through the Cleveland Clinic Transgender Surgery & Medicine Program at Cleveland Clinic Main Campus.

Inclusion Criteria:
- Age $\geq$ 18 years of age
- Patients scheduled for full-depth vaginoplasty surgery

Exclusion Critiera:
- Inability to speak or comprehend the English language
- Patients scheduled for no-depth vaginoplasty surgery
- Patients who have undergone previous PFPT

- Patients who are s/p prostatectomy or treatment for prostate cancer

STUDY INTERVENTIONS

Recruitment, Enrollment and Randomization

Patients scheduled to undergo vaginoplasty surgery at Cleveland Clinic Main campus will be approached about voluntary participation in this study. This will occur over the phone approximately one to three months before their scheduled surgery. Patients who agree to participate will be sent a consent form via the mail and will be asked to sign consent in person. Enrollment and randomization will occur following informed consent. All patients will be given a copy of their signed and dated consent.

Once enrolled, patients will be randomized into one of two groups:

- Postoperative PFPT
- No Postoperative PFPT

If patients are randomized into the Postoperative PFPT arm, they will be further randomized into the following sub-arms:

- Postoperative PFPT alone
- Preoperative and Postoperative PFPT

Surgery

All patients will undergo vaginoplasty surgery by a single surgeon in a standard fashion. The neovaginal cavity will be created using the same technique across all patients. Postoperative care will be routine and the same for all patients.

Postoperative Pelvic Floor Physical Therapy

There will be three possible PFPT regimens. All PT regimens will be performed by the same two physical therapists, trained in the management of patients who have undergone vaginoplasty surgery.

1) No PFPT

   Patients will present to see the physical therapist 3 weeks postoperatively. The following interventions will be performed:

   Subjective assessment of bowel and bladder function. Visual and external palpation and assessment of external pelvic floor region. Intravaginal pelvic floor

assessment. Pelvic floor muscle dynamics and coordination assessment. Review of pelvic floor anatomy and function.

2) Postoperative PFPT Only

Patients will present to see the physical therapist 3 weeks and 6 weeks postoperatively. The following interventions will be performed:

3 weeks:

- Subjective assessment of bowel and bladder function
- Visual and external palpation and assessment of external pelvic floor region
- Intravaginal pelvic floor assessment
- Pelvic floor muscle dynamics and coordination assessment
- Instruction of pelvic floor coordination and lengthening
- Discussion of dilator program and progression
- Home program with instructions

6 weeks:

- External scar assessment and treatment if tissue healing allows
- Instruction to patient of scar mobilizations
- Intravaginal pelvic floor assessment and treatment if indicated
- Review of pelvic floor lengthening and coordination
- Review and progression of dilator program if appropriate
- Assessment of current bowel/bladder symptoms; home program and instructions to address these symptoms

3) Preoperative PFPT and Postoperative PFPT

Patients will present to see the physical therapist 3 weeks before surgery, 3 weeks and 6 weeks postoperatively. The following interventions will be performed:

Preoperative:

- Diaphragmatic breathing
- Discuss dilator positioning/introduce dilator program
- External pelvic floor assessment
- Teach pelvic floor coordination
- Assessment of current bowel/bladder symptoms; home program and instructions to address these symptoms

3 weeks:

- Subjective assessment of bowel and bladder function
- Visual and external palpation and assessment of external pelvic floor region
- Intravaginal pelvic floor assessment
- Pelvic floor muscle dynamics and coordination assessment
- Instruction of pelvic floor coordination and lengthening
- Discussion of dilator program and progression
- Home program with instructions

6 weeks:

- External scar assessment and treatment if tissue healing allows
- Instruction to patient of scar mobilizations
- Intravaginal pelvic floor assessment and treatment if indicated
- Review of pelvic floor lengthening and coordination
- Review and progression of dilator program if appropriate
- Assessment of current bowel/bladder symptoms; home program and instructions to address these symptoms

Study Questionnaires & Exams

All patients will be administered questionnaires preoperatively and 12 weeks postoperatively. The following questionnaires will be administered:

Preoperatively:
- CRAD-8 and UDI-6
- PFIQ-7

Postoperatively 1 week (at the time of routine dilation teaching):
- Vaginal length (routine exam)

Postoperatively 12 weeks:
- CRAD-8 and UDI-6
- PFIQ-7
- PGI-I
- Ease of Passing Dilator (VAS 0-10)
- Pain with Dilation (VAS 0-10)
- Largest dilator size used
- Vaginal length (routine exam)

Cross-Over Treatment

Any patients in the No PFPT arm who are determined to have pelvic floor dysfunction or symptoms that may benefit from PFPT referral, will be referred after the 12-week mark. Any patient in one of the PFPT arms who is determined to still need PFPT for persistent pelvic floor dysfunction or symptoms will be referred for continued care.

DATA COLLECTION & MANAGEMENT

Data Collection:

In addition to the above-mentioned questionnaires and exam findings, the following data will be collected from the electronic medical record before surgery and 12 weeks postoperatively:

- MRN
- Age
- BMI
- Length of preoperative hormone therapy
- Previous orchiectomy
- Comorbid medical conditions: cardiac, pulmonary, diabetes, autoimmune
- Chronic pain: lower back pain, fibromyalgia, arthritis, other
- Intraoperative complications: bleeding, visceral injury, other
- Postoperative complications: wound issues, hematoma/seroma, infection, anatomic urinary stream issues, fistula, other
- PFPT utilization beyond 6 and 12 weeks postoperatively

Data Management:

Protection of each subject's personal health information will be a priority in this study. One master excel file containing subject personal information including name and medical record number will be kept in a password-protected file, on a designated protected research drive on a password-protected computer in a locked office at the Cleveland Clinic. In that file, each subject will be assigned a subject identification number that will be used for the purposes of data collection in order to de-identify subjects.

All paper forms used for data collection will be kept in a research cabinet dedicated to this project which will be locked at all times, in a locked office at the Cleveland Clinic. All forms will contain de-identified information – identification numbers will correspond to the subjects listed in the master excel file.

All study data will be transferred and managed electronically using REDCap (Research Electronic Data Capture). Each subject will be entered into REDCap using the assigned identification number from the master excel file. REDCap is a secure, web-based application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation, audit trials, and a

de-identified data export mechanism to common statistical packages. They system was developed by a multi-institutional consortium which was initiated at Vanderbilt University and includes the Cleveland Clinic. The database is hosted at the Cleveland Clinic Research Datacenter in the JJN basement and is managed by the Quantitative Health Sciences Department. The system is protected by a login and Secure Sockets Layers (SSL) encryption. Data collection is customized for each study as based on a study-specific data dictionary defined by the research team with guidance from the REDCap administrator in Quantitative Health Sciences at the Cleveland Clinic.

POWER ANALYSIS & STATISTICS

There will be 2 arms to this study: No Postoperstive PFPT and Postoperstive PFPT. The Postoperstive PFPT arm will be further randomized into two other arms: Postoperstive PFPT Only and Preoperative and Postoperative PFPT.

The primary aim is to compare the effectiveness of postoperative PFPT compared to no PFPT in transgender women undergoing vaginoplasty using Ease of Dilation (VAS 0-10) as the primary outcome. We determined that 17 subjects in each arm were needed to detect a difference of 2 (+/-1) points between the two groups (No Postoperstive PFPT vs Postoperstive PFPT) with 80% power and a significance level of 0.05. We will account for potential subject drop out and loss to follow-up as well as unforeseen factors in recruiting and will plan to recruit 20 subjects to each arm, for a total of 40 subjects.

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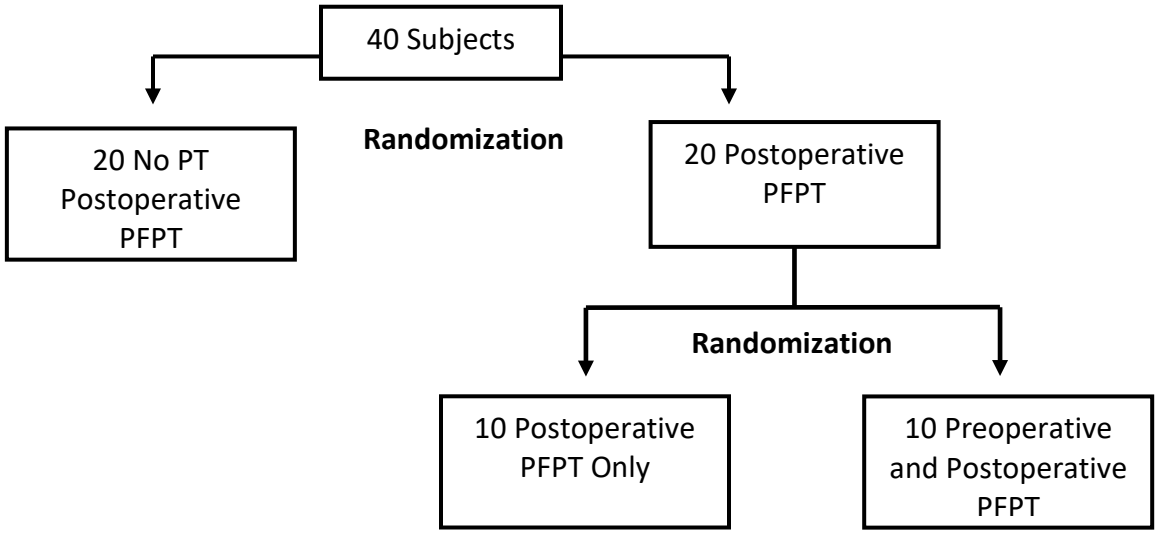

Continuous descriptive data will be reported as mean and standard deviation (±SD) or median with interquartile range (IQR), depending on distribution. Categorical data will be reported as frequencies, using percentages. Ease of dilation and pelvic floor symptoms will be compared between arms (No PFPT vs Postoperative PFPT). The investigators also plan to perform a subgroup analyses, comparing patients who

underwent postoperative PFPT only to those who underwent both preoperative and postoperative PFPT.

Ease of dilation (mean) and pelvic floor symptoms (mean difference from baseline) will be compared as a continuous variables using a student' t test to compare between the two groups. Binary logistic regression will be used to assess the influence of various patient factors on the patient reported ease of dilation as well as pelvic floor symptoms and results will be reported as odds ratios with 95% confidence intervals.

JMP 14.0 (SAS Institute Inc., Cary, NC) will be used for all statistical analyses. The primary investigator (CAF) will perform the statistical analysis. All results yielding $p < 0.05$ will be deemed statistically significant.

All analyses will be conducted using an intention-to-treat principle. The investigators anticipate that some non-adherence to the assigned intervention (e.g. crossover to the postoperative PFPT arm) may occur if patients are determined to be symptomatic requiring PFPT per the surgeon's discretion, and as these protocol deviations will bias the results towards superiority of the intervention, a per-protocol sensitivity analysis has also been planned.

REFERENCES

1) Masterson TA, Masterson JM, Azzinaro J, Manderson L, Swain S, Ramasamy R. Comprehensive pelvic floor physical therapy program for men with idiopathic chronic pelvic pain syndrome: a prospective study. Transl Androl Urol 2017;6(5):910-915.
2) Cohen D, Gonzalez J, Goldstein I. The Role of pelvic floor muscles in male sexual dysfunction and pelvic pain. Sex Med Rev 2016;4(1):53-62.
3) Straczynska A, Weber-Rajek M, Strojek K, et al. The impact of pelvic floor muscle training on urinary incontinence in men after radical prostatectomy (RP) – a systematic review. Clin Interv Aging 2019;14:1997-2005.
4) Jiang DD[1], Gallagher S, Burchill L, Berli J, Dugi D. Implementation of a Pelvic Floor Physical Therapy Program for Transgender Women Undergoing Gender-Affirming Vaginoplasty. Obstet Gynecol 2019; 133(5):1003-1011.
5) Manrique OJ, Adabi K, Huang TC, Jorge-Martinez J, Meihofer LE, Brassard P, Galan R. Assessment of pelvic floor anatomy for male-to-female vaginoplasty and the role of physical therapy on functional and patient-reported outcomes. Ann Plast Surg 2019;82(6):661-666.