Original Article

Role of allogeneic placental tissues in penile inversion vaginoplasty

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Background: The role of allogeneic placental tissue (APT) in genital gender-affirming surgery (GAS) is not well understood. Penile inversion vaginoplasty (PIV), the most common genital GAS, often results in tissue healing- or wound-related complications, including scarring and neovaginal stenosis. Surgical reoperation and revision vaginoplasty are common. The aim of this study was to evaluate the contribution of APT to postoperative outcomes in PIV.

Methods: The authors performed a retrospective analysis of consecutive adult patients undergoing primary PIV during a 6-year period (September 1, 2014 to September 1, 2020). Subjects receiving intraoperative application of an APT biomaterial were compared to those undergoing primary PIV without APT. Postoperative outcomes—including wound healing morbidity and reoperation—were compared between groups. Short- and long-term complications were classified using Clavien-Dindo.

Results: A total of 182 primary PIV cases were reviewed (115 conventional PIV; 67 PIV-APT). The postoperative follow-up time for the population averaged 12.7 months. All-cause and wound related complications were significantly lower amongst PIV-APT patients when compared to conventional PIV (P=0.002 and P=0.004, respectively). The rate of long-term complications was significantly lower in PIV-APT subjects: prolonged pain (P=0.001), prolonged swelling (P=0.047), and neovaginal stenosis (P<0.001). The PIV-APT group required significantly less reoperation for vaginal depth enhancement (P=0.007).

Conclusions: Though its use in urogenital reconstruction has been limited, this study indicates that the placement of APT during PIV significantly lowered the risk of complications associated with poor wound healing. This supports a novel use for placental tissues in reducing complications in genital GAS.

Keywords: Transgender; penile inversion vaginoplasty (PIV); wound healing; complications; placental allograft

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Introduction

Outcomes of successful gender-affirming procedures are associated with improved mental health and quality-of-life (QoL) in transgender or gender diverse (TGD) patients (1-3). Penile inversion vaginoplasty (PIV) is the most common genital gender-affirming surgery (GAS) done for TGD individuals (4). PIV involves deconstruction of the penis and scrotum followed by a reconstructive phase with clitoroplasty, vulvoplasty, urethral neomeatoplasty, and construction of a vaginal canal using a penoscrotal inversion flap and full thickness skin graft (5). The cosmetic and functional goals of vaginoplasty are to create an aesthetic vulva with erogenous clitoral sensation, downward directed urine stream, and a vaginal canal with the ability to engage in receptive penetration, if desired (6).

Suboptimal or compromised tissue healing contributes to various complications of PIV that impact sexual functioning (7-9). Wound dehiscence in areas of greatest tension (posterior introitus, posterior labia majora, apex of the vaginal canal) and tissue hypoxia lead to graft retraction, necrosis and tissue loss (10-14). Resultant intravaginal and external genitalia scarring can be hypertrophic, create strictures that obstruct the vaginal introitus, decrease vaginal depth, and reduce erogenous sensation (15,16). Neovaginal stenosis—symptomatic narrowing of the introitus and canal—and loss of vaginal depth occurs in as many as 45% of PIV cases (17,18). Maintaining canal patency, especially throughout the first year of recovery, is necessary to preserve neovaginal dimensions (13,19,20). This is commonly achieved through routine vaginal self-dilation. Prolonged pain, swelling, excessive granulation, and drainage result in poor compliance with routine self-dilation, limit receptive intercourse and are associated with an inability to achieve orgasm (7,8,21,22).

As many as 50–80% of patients request revision vaginoplasty to address aesthetic and functional concerns (13,22). Labiaplasty and/or clitoroplasty account for roughly one-third of cosmetic revisions (19,23). Various studies, including systemic reviews and meta-analyses, cite neovaginal stenosis as the leading contributor to non-cosmetic reoperation rates following gender-affirming vaginoplasty in roughly 60% of revisions (11,12,19,23). Management of neovaginal stenosis can be complex. Although numerous technical advances in PIV have improved vulvar aesthetics and vaginal apex creation, methods aimed at optimizing tissue repair and wound healing, which likely contribute to the development of stenosis, are lacking (5,24-29). Anecdotal reports in the literature include the use of skin substitutes in radial forearm free flap donor sites for gender-affirming phalloplasty; however, the use of biological grafts in transfeminine genital gender-affirming surgeries has not been thoroughly investigated (30,31).

Over the last century, the human placental membrane has been utilized to support the natural process of tissue repair in burn, trauma, chronic wounds, ophthalmology, sports medicine, dermatology, and reconstructive urology (32). Low immunogenicity, antimicrobial, anti-inflammatory, antifibrotic, and immunomodulatory properties make this biomaterial a useful adjunct in gender-affirming surgeries (33). Allogeneic placental tissue (APT) is a sterile human tissue product composed of dehydrated human amnion/chorion membrane (dHACM) in a powder form (Amniofill®, MiMedx Group Inc., Marietta, GA, USA). *In vitro*, APT has been associated with reductions in fibrotic gene expression and decreased alpha-smooth muscle actin—a stress filament responsible for contractile activity in scarring (34). Regulation of fibroblast activity and tissue fibrosis by APT has also been demonstrated in *ex vivo* models (34). APT is intended for the management of acute and chronic wounds. In the surgical setting, this allograft biomaterial acts as a scaffold to support cellular ingrowth and maintain a healing environment while slowly being resorbed by the body as the wounded tissues heal.

Highlight box

Key findings

- Penile inversion vaginoplasty with allogeneic placental tissue (PIV-APT) was associated with decreased tissue repair and wound healing complications compared to conventional PIV.
- Short-term complications were not impacted by the use of APT.
- Prolonged pain, swelling, and neovaginal stenosis were significantly lower in the PIV-APT cohort.
- Although reoperation rates were similar, PIV-APT required significantly less reoperation for vaginal depth enhancement.

What is known and what is new?

- APT has been previously demonstrated to support tissue repair in burn, trauma, and chronic wounds.
- This is the first study to employ human placental tissues in primary inversion vaginoplasty.

What is the implication, and what should change now?

- Placement of APT during PIV is associated with a lower risk of certain wound healing complications, suggesting its value as a useful adjunct to genital gender-affirming surgery.

The aim of this change-in-practice study was to evaluate the contribution of APT to the short- and long-term postoperative outcomes in consecutive PIV cases performed by a single surgeon. Focus was placed on incidence and risk factors associated with tissue repair and wound healing morbidity. The primary clinical endpoint was identified in this analysis as the surgical indication for revision vaginoplasty. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-420/rc).

Methods

Study design and cohort designation

This study applied a retrospective change-of-practice cohort design to evaluate short- and long-term tissue healing outcomes following primary PIV in a population of consecutive adult (≥18 years) patients operated on by the senior author. All of the patients in the study and their personal health information are sourced from Align Surgical Associates' medical records. All surgeries were performed by the senior author (T.S.) during a 6-year period (September 1, 2014, to September 1, 2020). Subjects receiving intraoperative application of an APT biomaterial to the dissected neovaginal canal space, the neovaginal canal lining, and to external genitalia incisions were compared to historical controls undergoing conventional PIV before availability of APT. Minimal depth vaginoplasty, revision vaginoplasty, penis-preserving vaginoplasty, vaginoplasty cases with concomitant negative pressure wound therapy (NPWT), and cases without a minimum 6-month follow-up in clinic were excluded from the primary analysis. After applying inclusion and exclusion criteria, 182 patients were identified within the study period (Figure S1).

All TGD individuals in this study met the World Professional Association for Transgender Health (WPATH) Standards of Care, Version 7, criteria for genital GAS prior to surgery (35). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board [Advarra (Columbia, MD) IRB Protocol No. Pro00031075] and informed consent was taken from all the patients prior to the time of operation.

Brief overview of surgical procedure

Primary PIV is a technically demanding operation. A detailed description of our approach has been published elsewhere (2,10). The lengthy procedure is performed under general anesthesia with the patient in lithotomy position. In short, once the perineum and scrotum are marked and incised, a full-thickness skin graft is created from the scrotal skin. A high ligation bilateral orchiectomy is carried out. The perineal body is then dissected at the base of the penis and the bulbospongiosus muscle is separated from the underlying urethra and debulked. Next, the prerectal space is dissected, creating a canal at the plane between the prostatic capsule and Denonvillier's fascia. A circumcising incision is performed on the penis, and the shaft is dissected from underlying erectile tissues above the tunica albuginea. The glans, its associated dorsal neurovascular bundle, the urethra, and the penile skin are carefully separated, and a vascularized penile skin flap is produced.

With midline ventral reduction of the glans, a neoclitoris is created from the island pedicle and sutured above the corpora cavernosa stump followed by urethrostomy and neoclitoris inset. The defatted and depilated scrotal skin is grafted to the distal aspect of the inverted penile shaft flap to create an appropriate extension of the vaginal lining and vault. The penile-scrotal skin is stented with insertion of a silicone dilator into the neovaginal canal. Once the neovaginal lining is placed into the previously dissected prerectal space, an antibiotic-covered gauze dressing is packed into the canal to act as a closely conforming bolster. Lastly, skin closure over a Penrose drain and imbrication of labia minora is followed by placement of a suture-reinforced surgical bolster over the entire site.

Surgical cases using APT received intraoperative placement of the biomaterial within the dissected neovaginal canal space, the neovaginal canal lining, and on the external genitalia incisions. The APT biomaterial employed is as a non-viable cellular powder stored at ambient conditions that does not require reconstitution. Its powdered form allows it to conform to irregular wound surfaces. A full 500-mg bottle of APT was directly sprinkled onto the wound bed of all subjects. All patients received the same postsurgical treatment regimens for follow-up, activity restrictions, dilation, and site care.

Variables of interest

Deidentified subject-level characteristics included: (I) demographics: age at the time of operation, race, ethnicity, body mass index (BMI) in kg/m^2; and (II) baseline medical history: years on hormone replacement therapy (HRT),

Charlson Comorbidity Index (CCI) grouping and score with estimation of 10-year survival based on aggregate comorbidities, human immunodeficiency virus (HIV) status, and smoking status. Postoperative complications were categorized and stratified according to severity using a standardized grading system: (I) all-cause: urethral injury, rectal injury, hematoma formation, blood transfusion, pulmonary embolus, neovaginal prolapse, rectovaginal fistula, urinary retention with catheter reinsertion, loss of sensation, dyspareunia, hypersensitivity, anorgasmia, urinary issues (incontinence or splayed urinary stream), and excessive erectile tissue; and, (II) complication subtype related to tissue repair and wound healing, defined in this study as: (i) short-term events (0–6 months): surgical site infection (SSI), wound breakdown with necrosis, and excessive granulation tissue with vaginal drainage; and, (ii) long-term-term conditions (>6–12 months or greater): prolonged swelling, prolonged pain, excessive scarring, neovaginal (canal and introitus) stenosis, introital stenosis only, and urethral stenosis. In cases undergoing reoperation, the indication (cosmetic versus non-cosmetic)—clitoroplasty, labiaplasty, and vaginal lengthening—was assessed as the primary clinical endpoint. Neovaginal stenosis was initially reported by the patient and then confirmed clinically as a loss of depth or formation of internal strictures in the neovaginal canal. The length of surgeon's cumulative experience—defined as the total number of days experience at the time of patient surgery—was calculated for each individual.

Modified Clavien-Dindo

Unique to gender-affirming reconstruction and plastic surgery, the disposition of aesthetic and functional complications requires assessment at 6 months or greater. Reoperation for labiaplasty, clitoroplasty, and vaginal lengthening are typically done 8–12 months following the primary PIV surgery. The conventional Clavien-Dindo offers a standardized grading system (I through V) based on the intervention required to manage acute complications following surgery (36,37) (Table S1). This grading system applies only to the acute postoperative period. Therefore, a modified Clavien-Dindo classification with the addition of Grade IIIc: long-term was used to capture complications that required intervention under anesthesia at a later stage of care. Minor modifications to Clavien-Dindo such as this have been reported throughout the literature by other surgical specialties to account for nuanced postoperative courses that require long-term follow-up and management (38-40).

Statistical analysis

Continuous variables were reported as either means with standard deviations or medians with 25th and 75th percentiles. Differences in values were tested using the Student's *t*-test or Mann-Whitney *U* test where applicable based on complete-case analysis. Categorical data were summarized as proportions and between group differences were assessed using Chi-square or Fisher's exact test. Logistic regression models were developed to identify the univariate risk factors associated with post-vaginoplasty morbidity. All variables were assessed for collinearity and included in multivariable Poisson regression models. To determine predictors of postoperative morbidity and reoperation, measures of association between the multiple risk factors and our dichotomous outcomes of interest were estimated using risk ratio (RR) [RR; 95% confidence interval (CI)]. All tests were two-tailed and a P level of <0.05 was recognized as statistically significant. The statistical software program SAS/STAT® v9.4 (SAS Institute Inc., Cary, NC, USA) performed all study computations.

The following null hypotheses (NHs) were put forth *a priori*: there is no significant difference in postoperative morbidities related to tissue repair and wound healing between groups (H_{0a}), there is no significant relationship between predictor variables and the risk for developing tissue repair/wound healing morbidity (H_{0b}), or the risk of requiring revision vaginoplasty for or including vaginal length enhancement (H_{0c}).

Results

Cohort characteristics

The sample included a total of 182 primary PIV patients (115 conventional PIV patients and 67 PIV-APT patients). Baseline subject-level characteristics for each group are listed in *Table 1*. Patients were predominantly White (64.8%); 8.2% were Black or African American, and 5.0% Asian. While PIV-APT patients were significantly younger, there were no differences in BMI, length of HRT, or comorbidity burden (per CCI scores) between the groups.

Postoperative morbidity

The postoperative follow-up time for the population

Table 1 Baseline subject characteristics

Characteristics	PIV (n=115)	PIV-APT (n=67)	P value
Age (years)			
Mean ± standard deviation	37.6±12.0	32.7±10.7	
Median (25^{th}, 75^{th} percentiles)	34.6 (27.3, 46.2)	29.9 (24.7, 37.5)	0.007
Race, n (%)			0.13
Asian	3 (2.6)	6 (9.0)	
Black or African American	10 (8.7)	5 (7.5)	
White	66 (57.4)	52 (77.6)	
Other	14 (12.2)	4 (6.0)	
Missing	22 (19.1)	0 (0.0)	
Ethnicity, n (%)			0.15
Hispanic	15 (13.0)	15 (22.4)	
Non-Hispanic	100 (87.0)	52 (77.6)	
BMI (kg/m^2)			
Mean ± standard deviation	24.2±7.5	24.4±4.0	
Median (25^{th}, 75^{th} percentiles)	24.0 (21.7, 28.4)	23.7 (21.5, 27.0)	0.56
Duration of HRT (years)			
Mean ± standard deviation	5.3±6.2	5.3±4.6	
Median (25^{th}, 75^{th} percentiles)	2.9 (1.8, 6.1)	4.1 (2.3, 6.6)	0.10
CCI group, n (%)			0.57
Group 1 (0 points)[†]	89.0 (77.4)	55.0 (82.1)	
Group 2 (≥1 points)[‡]	26.0 (22.6)	12.0 (17.9)	
CCI score (points)			
Mean ± standard deviation	0.4±0.8	0.3±0.7	
Median (25^{th}, 75^{th} percentiles)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.43
CCI estimated 10-year survival (%)			
Mean ± standard deviation	96.5±4.6	96.9±4.6	
Median (25^{th}, 75^{th} percentiles)	98.3 (98.3, 98.3)	98.3 (98.3, 98.3)	0.43
Other medical history, n (%)			
HIV	8 (7.0)	1 (1.5)	0.16
Current smoker	18 (15.7)	4 (6.0)	0.06

[†], 0 comorbidities and aged <50 years; [‡], at least 1 comorbidity and/or ≥50 years. PIV, penile inversion vaginoplasty; APT, allogeneic placental tissue; BMI, body mass index; HRT, hormone replacement therapy; CCI, Charlson Comorbidity index; HIV, human immunodeficiency virus.

Table 2 Summary of postoperative morbidity and classification of complication type

Outcome	PIV (n=115)	PIV-APT (n=67)	P value
Experienced zero complication, n (%)	37 (32.2)	30 (44.8)	0.11
Complications per patient, all-cause[†]			
Mean ± standard deviation	2.1±2.2	1.1±1.5	
Median (25^{th}, 75^{th} percentiles)	2.0 (0.0, 4.0)	1.0 (0.0, 2.0)	0.002
Experienced ≥3 all-cause complications, n (%)	42 (36.5)	7 (10.4)	<0.001
Complications per patient, tissue and wound			
Mean ± standard deviation	1.3±1.5	0.6±1.0	
Median (25^{th}, 75^{th} percentiles)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.004
Experienced ≥3 tissue and wound complications, n (%)	25 (21.7)	3 (4.5)	<0.001
Classification			
Short-term: 0–6 months, n (%)			
Surgical site infection	3 (2.6)	0 (0.0)	0.30
Wound breakdown with necrosis	20 (17.4)	8 (11.9)	0.40
Granulation tissue with vaginal drainage	7 (6.1)	2 (3.0)	0.49
Long-term: 6–12 months or greater, n (%)			
Prolonged swelling	16 (13.9)	3 (4.5)	0.048
Prolonged pain	22 (19.1)	2 (3.0)	0.001
Excessive scarring	11 (9.6)	3 (4.5)	0.26
Neovaginal stenosis	24 (20.9)	0 (0.0)	<0.001
Introital stenosis only	8 (7.0)	2 (3.0)	0.33
Urethral stenosis	0 (0.0)	0 (0.0)	–

See Table S2 for details regarding all-cause complications. [†], intraoperative, postoperative acute and long-term complications. PIV, penile inversion vaginoplasty; APT, allogeneic placental tissue.

averaged 12.7 months. A summary of all-cause and subtype complications is depicted in *Table 2*. The rate of all-cause and tissue repair/wound related complications per patient was significantly lower amongst PIV-APT patients when compared to conventional PIV. Similarly, a significantly greater proportion of the conventional PIV group experienced ≥3 all-cause complications (P<0.001) and ≥3 tissue repair/wound healing complications (P=0.001). For acute postoperative complications, significantly more hematomas and bleeding were observed in the conventional PIV group (P=0.004) (see Table S2).

Regarding specific tissue repair/wound healing indices, there were no significant differences noted between groups for short-term outcomes: SSI (P=0.30), excessive wound breakdown with necrosis (P=0.40) or excessive granulation tissue with drainage (P=0.50). Certain long-term complications (lasting >6 months) were identified as significantly lower in PIV-APT subjects: prolonged pain (P=0.001), prolonged swelling (P=0.048), and neovaginal stenosis (P<0.001).

Details for reoperation are shown in *Table 3*. Both groups expressed similar rates of aesthetic dissatisfaction with postoperative results (P=0.12) and underwent similar rates of revision vaginoplasty (P=0.09). However, neovaginal stenosis was the primary indication for revision vaginoplasty in a significantly greater proportion of conventional PIV subjects (27.6%) compared to PIV-APT counterparts (4.2%) (P=0.02). Overall, the PIV-APT groups required significantly less reoperation for vaginal depth enhancement (P=0.007). Nevertheless, both groups had similar rates of

Table 3 Reoperation and revision vaginoplasty

Outcome	Total (n=182)	PIV (n=115)	PIV-APT (n=67)	P value
Expressed aesthetic dissatisfaction, n (%)	48 (26.4)	35 (30.4)	13 (19.4)	0.12
Underwent PIV revision, n (%)	83 (45.6)	58 (50.4)	25 (37.3)	0.09
Primary indication for revision performed, n (%)				
Clitoroplasty and labiaplasty	17 (20.7)	9 (15.5)	8 (33.3)	0.08
Neovaginal stenosis	17 (20.7)	16 (27.6)	1 (4.2)	0.02
Any vaginal depth enhancement	25 (30.5)	23 (39.7)	2 (8.3)	0.007

Revisions included vaginal lengthening in addition to other procedures, e.g., clitoroplasty, labiaplasty, urethromeatoplasty. Indications for revision are reported as percentages of patients who underwent revision, not of the entire study cohort. PIV, penile inversion vaginoplasty; APT, allogeneic placental tissue.

Table 4 Predictors of postoperative morbidity and reoperation

Factor	≥3 wound healing complications		Prolonged pain and swelling		Neovaginal stenosis		Vaginal depth enhancement	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Surgeon experience	1.000 (0.997, 1.002)	0.64	0.999 (0.998, 1.002)	0.88	0.999 (0.997, 1.001)	0.42	0.997 (0.995, 1.00)	0.04
PIV without APT	4.78 (1.39, 16.36)	0.01	4.14 (1.40, 12.24)	0.01	9.80 (2.18, 44.04)	0.003	11.45 (2.55, 51.45)	0.002
Age	1.01 (0.97, 1.06)	0.41	1.01 (0.97, 1.05)	0.44	1.01 (0.97, 1.05)	0.56	1.02 (0.97, 1.07)	0.32
BMI	0.98 (0.83, 1.17)	0.89	1.12 (0.95, 1.31)	0.16	0.94 (0.78, 1.12)	0.53	0.85 (0.45, 1.66)	0.25
HRT duration	1.01 (0.95, 1.06)	0.73	0.98 (0.91, 1.05)	0.63	0.97 (0.90, 1.04)	0.51	0.98 (0.91, 1.06)	0.70
Current smoker	1.26 (0.49, 3.19)	0.62	2.39 (1.14, 4.99)	0.02	1.39 (0.55, 3.56)	0.48	1.48 (0.56, 3.87)	0.42
Comorbidities	0.74 (0.39, 1.39)	0.35	0.57 (0.27, 1.22)	0.15	1.13 (0.67, 1.91)	0.63	0.87 (0.45, 1.66)	0.68

RR, relative risk; CI, confidence interval; PIV, penile inversion vaginoplasty; APT, allogeneic placental tissue; BMI, body mass index; HRT, hormone replacement therapy.

reoperation for clitoroplasty and labiaplasty (P=0.08).

Predictors of reoperation

Table 4 depicts multivariable analysis of morbidity and non-cosmetic surgical reintervention-related factors. Conventional PIV was associated with nearly 5 times greater risk of developing multiple tissue repair and wound healing complications (RR =4.78; 95% CI: 1.39–16.36; P=0.01) and prolonged pain and swelling (RR =4.14; 95% CI: 1.40–12.24; P=0.01). Patients undergoing PIV without adjunct APT were nearly 10 times more likely to develop neovaginal stenosis (RR =9.80; 95% CI: 2.18–44.04; P=0.003), and over 11 times more likely to need reoperation for vaginal depth enhancement (RR =11.45; 95% CI: 2.55–51.45; P=0.002). Current smokers (versus former and never) were also at greater risk of prolonged pain and swelling (RR =2.39; 95% CI: 1.14–4.99; P=0.02). Surgeon's cumulative experience was negatively associated with a one-fold greater risk of undergoing a reoperation that included vaginal length enhancement (RR =0.997; 95% CI: 0.995–1.00; P=0.04), but was not significantly associated with development of neovaginal stenosis, development of pain and swelling, or >3 wound complications.

Clavien-Dindo classification

Grade 1 complications were observed in 58.3% of the conventional PIV group and 46.3% in PIV-APT (P=0.13). The incidence of Grade II complications was 9.6% and

6.0%, conventional PIV versus PIV-APT, respectively (P=0.58). The difference in Grade IIIb complications was significant as 12% of the conventional PIV group required acute postoperative intervention under general anesthesia compared to zero PIV-APT patients (P=0.002). Grade IIIc—long-term complications that required intervention under anesthesia—were similar between groups (P=0.07). There were no Grade IV and V complications observed in this study (see Table S3).

Discussion

PIV is the most commonly performed gender-affirming genital surgery. Despite its high post-operative satisfaction rate, PIV is associated with known complications, including poor wound healing and neovaginal stenosis, often necessitating revision surgery. Prior work has identified some risk factors for developing these complications, but technique-based interventions to prevent them have not been well described (10). The field of wound healing has a prolific and expansive research landscape, largely focusing on improving outcomes following large injuries with significant tissue loss (e.g., burns and grafts). Among the methods to improve the healing process are matrix replacements, such as PIVs, that provide scaffolding for delicate, healing tissue and allow for optimal regrowth. This study assesses the potential for APT, a commercially-available cryopreserved tissue product, to improve the wound healing process in patients undergoing PIV.

Our study found that, though reoperation rates in the two groups were similar, individual indications varied. While the PIV group had significantly more wound-healing-related re-operations compared to the PIV-APT group (i.e., stenosis repair and vaginal depth enhancement), there were no differences in aesthetic revisions. The PIV-APT cohort displayed lower rates of certain wound healing complications, including prolonged pain and swelling, as well as neovaginal stenosis, although no differences in the rate of infection, wound breakdown or excessive scarring were identified. This suggests that placement of APT may lower the risk of certain complications associated with poor wound healing, which aligns with prior literature on its use in surgical procedures, though its use in urogenital reconstruction has been limited. Clinically, APT and similar placental-derived tissues have been shown to improve chronic wound closure in diabetic foot ulcers and spina bifida closures, and are equally effective when compared to a split-thickness skin graft in a single radial forearm free flap coverage trial (41-43). An allograft matrix product has been successfully used in gender-affirming vaginoplasty in one published report, though the group did not use a penile inversion technique and seeded the product with patients' own fibroblasts prior to implantation (44). Both cohorts in our study demonstrated similar levels of aesthetic dissatisfaction, consistent with previous research suggesting that aesthetic concerns remain the primary reason for revision vaginoplasty (10). That said, our study did not identify differences in the overall revision rate, and thus, surgeons should not view the use of APT as a single solution to the high revision rates seen in vaginoplasty.

Previous literature describing the use of amnion grafts in vaginoplasty focuses on its use in vaginal hypo- or aplasia due to Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (aka Müllerian agenesis) (45). Surgical intervention involves formation of the vaginal canal using a placental allograft matrix, which results in reduced postoperative pain, infection, and scarring (46,47). However, our study employs an allograft in the form of a powder that is applied to the tissue intraoperatively. Little has been studied about this form of APT, though our results suggest the viability of allograft powder products in neovaginal construction and demonstrate the usefulness of APT, specifically in PIV, for decreasing postoperative complications, many of which are related to improper wound healing (48). The regenerative mechanism of APT is likely due to a combination of growth factors contained in the product (endothelial growth factor, fibroblast growth factor), regulation of inflammation by the anti-inflammatory cytokines IL-4, -6, and -10, as well as inhibition of metalloproteinase activity (49). APTs have also been shown to improve recruitment of progenitor cells and promote angiogenesis, although most research in this arena has been conducted in murine dermal *in vivo* models (50,51).

Strengths of this study include the patient volume and relative consistency of operative technique, as a single-surgeon, single-institution study. Limitations include possible variation in APT quantity or location of its application among patients, and between-group differences in characteristics that may affect wound healing. Age was found to be statistically higher in the conventional group compared to the APT cohort. which may explain the higher rate of wound complications due to an age-related decline in angiogenic capacity. Smoking status and HIV status were not found to be statistically different between groups. Furthermore, this study may have been underpowered to detect the differences in reoperation rates and indications

between groups, and we did not query specific reasons for aesthetic dissatisfaction in patients undergoing revisions for that reason. We also did not specifically trend or compare charges for the primary PIV procedure (with and without use of APT). Though differences related to the material cost for APT may exist between groups, such data was not captured in the current analysis, as the cost ($750 for a 500-mg bottle) was included in the facility fee. Additionally, the results of the present study were limited by its retrospective nature, including selection and information bias. The authors were unable to access certain data for some patients in the cohort, such as operative times and intraoperative vaginal canal measurements, which may have impacted the reoperation rate. As a complex procedure, PIV has a steep learning-curve, influenced by surgeon training and experience. Due to the retrospective nature of the study, we cannot ascertain the individual contribution of surgeon experience to the final result. A separate, prospective randomized clinical trial is needed to isolate the effect of APT in PIV.

Insurance coverage for GAS is denied in up to 55% of patients, and half of all patients with coverage for surgery live out of network for surgeons trained in gender-affirming procedures (52,53). Transgender patients often face barriers to insurance coverage for all gender-affirming care, including surgery, and are almost three times more likely to live in poverty than the general population (54). Cost is an important factor we believe should be answered by future research, as it can influence decision-making by providers and institutions considering the implementation of APT in PIV. In our practice, the cost of APT is covered by the facility fee in the patient's bill, but this may not be possible in all practices. We hypothesize that the higher upfront cost of using APT may offset by the reduction in subsequent medical care and revision operations due to significantly reduced inflammation, pain, swelling, and stenosis. This hypothesis is supported by prior work demonstrating cost-effectiveness of APT in the treatment of diabetic foot ulcers (55,56). The relatively small cohort size in our study prevented a true cost analysis, which should be done in follow-up studies.

This study introduces GAS, particularly PIV, as an application of wound healing and allograft use, and further opens the door to additional uses of APT and similar products in other gender-affirming procedures. Previous work has suggested its utility in urologic reconstructive surgery, but further research is needed to assess its viability in gender-affirming phalloplasty and metoidioplasty using current surgical techniques (57). Major complications resulting from the use of APT and similar materials have not been reported thus far and were not seen in our study.

Novel surgical techniques and applications of existing regenerative technologies are needed in the field of GAS to optimize patient outcomes. Although PIV remains the most widely used technique, several modifications exist. Peritoneal vascularized flap vaginoplasty is an emerging procedure that has been demonstrated to augment the neovaginal apex and canal (58). The peritoneum's high elasticity and lubricating properties make it a promising candidate for extension of the neovagina (59). This technique is particularly effective during primary vaginoplasty in case of lack of genital skin or as a secondary technique to repair stenosis due to scarring secondary to ischemia or infections (60). However, this technique has not been widely adopted yet due to the need for advanced surgical expertise. In a field as sensitive as genital reconstruction, complications can significantly affect quality of life. Therefore, the use of APTs represents a promising technique for improvement of patient outcomes in genital GAS.

Conclusions

The addition of APTs during primary inversion vaginoplasty was associated with decreased wound-healing-related re-operations. Although overall reoperation rates were not impacted by the use of APTs, long-term complications such as prolonged pain, swelling, and neovaginal stenosis were markedly decreased. This is the first study to explore the novel role of human placental-derived tissues in PIV.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board [Advarra (Columbia, MD) IRB Protocol No. Pro00031075] and informed consent was taken from all the patients prior to the time of operation.

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