Ovine Forestomach Matrix Implant for Surgical Management in Perianal Fistulas: A Retrospective Case-Series

Vinesh Anandarajan

vinesh.anandarajan@gmail.com

Vassar Brothers Medical Center

Pranat Kumar

Vassar Brothers Medical Center

Kathryn Wells

Vassar Brothers Medical Center

John Choi

Vassar Brothers Medical Center

Research Article

Keywords: Anal fistula, extracellular matrix, fistula plug, ovine forestomach matrix, perianal fistulas

Posted Date: July 10th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4607116/v1

Additional Declarations: Competing interest reported. Pranat Kumar and John Choi are consultants for Aroa Biosurgery Limited.

Abstract

Background

Surgical management of perianal fistula (PF) is complicated by a high rate of recurrence and risk of damage to the sphincter complex. Advances in surgical techniques and the use of traditional and biologic fistula plugs have demonstrated recent success. However, the need for minimally invasive, cost-effective techniques capable of lower recurrence rates still exists. Ovine forestomach matrix (OFM) is a biologic graft capable of regenerating healthy native tissue and was used for the surgical management in PFs in this study.

Methods

This retrospective case-series analyzed data collected from 25 patients at a single site treated with OFM for various perianal fistula subtypes as a key component of the surgical treatment algorithm. The primary outcome was healing status at 12 weeks. Secondary outcomes included time to complete closure, recurrence at follow-up intervals, and post-operative complications.

Results

The most common PF subtype was a trans-sphincteric fistula (72%) and of primary and cryptoglandular origin. Mean PF depth was 3.3 ± 1.6 cm with a 76% incidence of healing at 12-weeks and a median time to closure of 4.5 weeks (IQR: 4.0, 6.0). At last follow-up, 21 of 25 PFs were completely healed (84%) with one recurrence at a median follow-up time of 25 weeks (IQR: 15.5, 29.5). Eighty percent of patients reported no pain at post-operative follow-up.

Conclusion

OFM was found to be a safe, efficacious, and cost-effective treatment for the surgical management of perianal fistula. At last follow-up, OFM achieved successful closure with no recurrences using a median single device implantation.

Introduction

The primary goal of surgical management of perianal fistula (PF) is to eradicate any existing infection and promote definitive closure of the fistula tract without compromising the function of the sphincter complex. With current surgical management techniques, successful treatment of PFs remains a challenge due to high recurrence rates and the potential for injury to the sphincter complex, which can result in incontinence [1, 2]. This problem is compounded due to the number of PFs associated with inflammatory bowel disease, including Crohn's disease [3] and ulcerative colitis [4], which can result in

complex fistulas that often require a multidisciplinary approach [5]. These challenges will continue to grow due to the chronic nature of these disease states and their increasing global prevalence [6]. However, perianal abscess remains the overwhelming contributing factor in the pathogenesis of PFs. Importantly, the incidence of the disease states may be underreported due to social stigma associated with the condition. This combination of factors presents a need for surgical advances in the management of PFs.

Currently, invasive surgical procedures such as ligation of inter-sphincteric fistula tract (LIFT) and mucosal advancement flaps, offer high clinical efficacy, but still carry a risk of post-operative complications, including infection, bleeding, or anal sphincter damage [7, 8]. Less invasive techniques, such as fibrin glue injection and traditional fistula plugs, minimize these complications but often result in poor closure rates and a high recurrence rate [9, 10]. More recently, surgical management advances have included techniques that incorporate video-assisted procedures in an attempt to limit incontinence associated with injury to the sphincter complex [11]. Similarly, ablative techniques have demonstrated success in mitigating sphincter damage but carry a high recurrence rate with moderate clinical efficacy [12, 13]. Stem cell therapies have also shown value, particularly with respect to fistulas related to Crohn's disease, but future studies evaluating PFs of other etiologies are needed [14, 15].

Therefore, a need still exists for a minimally invasive, clinically effective, simple, and cost-effective alternative to traditional surgical interventions for PF. This has led many surgeons to explore regenerative biomaterials as a treatment option, such as biologic anal fistula plugs [16, 17]. Biological implant materials, in both allograft and xenograft form, have seen adoption in PF management [18, 19]. However, the goal of many fistula plugs is to provide a method of occluding the fistula alone without a specific focus on augmenting tissue regeneration. For this reason, biologic fistula plugs have demonstrated success in limiting incontinence and surgical complications but exhibit varying degrees of clinical efficacy. More recently, a biologic implant derived from ovine forestomach matrix (OFM) has been studied as a novel alternative to the traditional plugs with promising early success [20]. OFM is a decellularized extracellular matrix (dECM) that preserves inherent tissue architecture and retains biomolecules crucial to the tissue regeneration process [21]. In this study by Hsu et al, 14 patients received OFM as a perianal fistula implant (PAFI) and were followed for a median 37.6 ± 20.1 weeks. Of the 78.6% (n = 11/14) of patients that healed during the study, median time to complete closure was 3.6 weeks. Only two patients in the study required an additional OFM PFAI procedure and no adverse events or post-operative infections were reported.

In addition to its preliminary success as a PAFI, OFM may serve as an ideal implant device due to its ability to function in an inflammatory and contaminated environment. OFM devices have been show to modulate wound proteases in preclinical [22] and clinical studies [23] and may be particularly effective in the inflammatory environment present in PFs. Additionally, OFM has demonstrated the ability to recruit mesenchymal stromal cells [24], stimulate cell proliferation and angiogenesis [25], all of which are key components of tissue regeneration. OFM has been further employed in the regeneration of multiple types of contaminated soft tissue defects, in addition to the recent use as a PAFI [20, 26–29]. The

combination of initial clinical efficacy in PFs and in other contaminated, inflammatory tissues has led the authors to perform a larger single-center, retrospective case series to validate the previously published PAFI pilot study in a new, larger patient population. OFM was evaluated as a PAFI to facilitate closure, minimize post-operative complications, and negate the need for more invasive surgical interventions.

Methods

The study protocol was reviewed by the Nuvance Health Institutional Review Board, and ethical oversight of the retrospective study was waived. The study was conducted in accordance with institutional guidelines and the World Medical Association Declaration of Helsinki ethical guidelines. All patient information, including any patient images, was de-identified for research purposes. All patients signed written informed consent for the procedure.

Data were collected and retrospectively analyzed from patients that met the inclusion and exclusion criteria (Table 1) and represented consecutive patients that had undergone a minimally invasive PAFI using OFM between July 2021 and October 2023. OFM graft (Myriad Matrix™ Soft Tissue Bioscaffold, Aroa Biosurgery Limited, Auckland, New Zealand) and/or micronized OFM (Myriad Morcells™, Aroa Biosurgery Limited, Auckland, New Zealand) were used according to the instructions for use. Preoperative MRI was obtained for surgical planning when appropriate. Patients received general anesthesia or monitored anesthesia care for the surgical procedure. Local anesthesia was administered using 1% lidocaine as a bilateral pudendal nerve and/or circumferential perianal nerve block. The fistula tract was first debrided with a curette to remove epithelial tissue lining the fistula. The OFM device was hydrated with saline, then hand rolled to create a cylindrical implant. The OFM device size was determined based on the length and diameter of the fistula tract (either 5x5 cm or 7x10 cm and 3-layer for narrow diameter and 5-layer for wider diameter). Any remaining space in the defect was filled with OFM particulate. The OFM implant was introduced into the fistula tract and then secured at the internal and external opening with absorbable polydiaxonone sutures (PDS) in a U-stitch technique. Additional local anesthesia was administered at the conclusion of the case for pain control. Postoperative dressing of Xeroform® and gauze was then applied. Time to heal was determined by clinical evaluation and defined as no sign of drainage, open wound, or surrounding infection. Positive drainage of fecal material or air through the external opening was a clinical sign of recurrence.

Table 1
Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Male or female patients age > 18-years old	Patients still under active management having received their PF treatment < 3 months prior
Patients with a primary or recurrent PF (cryptoglandular disease) treated with OFM graft and/or OFM particulate as part of their surgical intervention	Patients that did not receive OFM graft and/or particulate as part of their PF treatment
	Patients with inflammatory bowel disease

Patient demographics (e.g. age, gender, significant baseline comorbidities, Park's Classification), prior surgical interventions and outcomes (e.g. complete healing, recurrence, complications) were captured in Excel® (Microsoft Corporation). The primary study outcome was defined as complete healing at post-operative week 12. Secondary endpoints included median time to complete healing, recurrence of fistula during the follow up interval, and post-operative complications (e.g. infection, pain, and recurrence). Descriptive statistics (e.g., median, mean, standard deviation (SD)) were computed using Excel®.

Results

A total of 25 participants were included in this case series. Twenty patients were male, and 5 patients were female with a mean age of 48.3 ± 14.9 years (Table 2). The majority of participants presented with medical co-morbidities (80%), with obesity (64%) and hypertension (44%) being the most common (Table 2). One patient had a prior history of colon cancer. Four patients had intersphincteric fistulas (16%), 18 patients had transsphincteric (72%), and 3 patients had extrasphincteric defects (12%) (Table 3). A prior history of cryptoglandular infection occurred in 23 of 25 patients (92%). Sixty percent of PFs were primary and 40% were recurrent fistulas. The mean PF depth was 3.3 ± 1.6 cm (median, 3.5 (IQR: 2.3, 4.0). Most patients had prior surgical intervention: fistulotomy (48%, n = 12/25), incision and drainage (I&D) (28%, n = 7/25), LIFT (8%, n = 2/25), and a single patient had a previous colostomy. Two patients had two prior fistulotomies and two patients had two prior I&D procedures. A total of 13 patients (52%) had pre-operative seton placement for a median duration of 35.0 weeks (IQR: 16.0, 47.5) (mean, 39.5 ± 32.4). The median OFM implant application was 1.0 (IQR: 1.0, 1.0) (mean, 1.1 ± 0.3) (Table 3).

Table 2
Patient Demographics

Characteristic	Value
Participants (n)	25
Age (mean ± SD) [median, (IQR)]	48.3 ± 14.9 [36, (38, 58)]
Gender	
Male, % (n)	80.0% (20)
Female, % (n)	20.0% (5)
Complicating co-morbidities, % (n)	80% (20)
DM	12.0% (3)
Hypertension, % (n)	44.0% (11)
Obesity, % (n)	64.0% (16)
Afib, % (n)	8.0% (2)
CAD, % (n)	8.0% (2)
OSA, % (n)	8.0% (2)
COPD, % (n)	16.0% (4)
HLD, % (n)	16.0% (4)
Constipation, % (n)	8.0% (2)
Colon cancer, % (n)	4.0% (1)

Abbreviation: n, sample size; SD, standard deviation of the mean; IQR, interquartile range; DM, diabetes mellitus; Afib, atrial fibrillation; CAD, coronary artery disease; OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; HLD, hyperlipidemia

Table 3
Baseline Anal Fistula Characteristics and Operative Technique

Characteristic	Value
Type of fistula, % (n)	25 (100%)
Intersphincteric, % (n)	16.0% (4)
Transsphincteric, % (n)	72.0% (18)
Extrasphincteric, % (n)	12.0% (3)
Fistula depth (mean ± SD), [median (IQR)] (cm), (n)	3.3 ± 1.6, [3.5 (2.3, 4.0)], (25)
Primary or recurrent fistula, % (n)	
Primary, % (n)	60.0% (15)
Recurrent, % (n)	40.0% (10)
Prior surgical intervention, % (n)	68.0% (17)
Fistulotomy, % (n)	48.0% (12) (8.0%, (n = 2) had undergone two prior fistulotomies)
I&D, % (n)	28.0% (7) (8.0% (n = 2) had undergone two prior I&D)
LIFT, % (n)	8.0% (2)
Colostomy, % (n)	4.0% (1)
Prior cryptoglandular infection, % (n)	92.0% (23)
Prior seton use, % (n)	52.0% (13)
Pre-operative seton duration (weeks), median (IQR), [mean ± SD], (n)	35.0 (16.0, 47.5), [39.5 ± 32.4], (13)
Pre-operative pain, % (n)	48.0% (12)
Product applications, median (IQR), [mean ± SD], (n)	1.0 (1.0, 1.0), [1.1 ± 0.3], (25)

Abbreviations: n, sample size; SD, standard deviation of the mean; IQR, interquartile range; I&D, incision and drainage; LIFT, ligation of intersphincteric tract

The median time to heal was 4.5 weeks (IQR: 4.0, 6.0) (mean, 6.1 ± 5.0). At 12-weeks, 19 patients remained healed (76%), 3 patients were not healed (12%), 2 patients had unreported data (8%), and 1 patient had a PF recurrence (4%). The median follow-up time was 25 weeks (IQR: 15.5, 29.5) (mean, 24.4 ± 14.3). Outcomes at last follow-up were 21 patients remained healed (84%), 4 patients were not healed (16%), and one recurrence that underwent a second application of OFM and healed uneventfully at 5.5

weeks. The single patient with a recurrence remained healed at last follow-up. Preoperative pain was reported in 12 patients (48%) and decreased to 5 patients reporting pain postoperatively (20%). There were no postoperative complications or adverse events reported.

Discussion

The optimal surgical management for PFs is debated due to a combination of high recurrence rates, the risk of incontinence associated with more invasive procedures, and recent advances in surgical techniques. The goal remains to achieve high closure rates with a minimally invasive procedure that minimizes the risk of damaging the sphincter complex while limiting the recurrence rate. With no consensus on a standard surgical approach, traditional and biologic fistula plugs, or implants, have been an increasingly common reported solution [9]. In this study, OFM was used as a PAFI due to its demonstrated ability to augment healthy soft tissue regeneration in chronic defects, its ease of use, low cost, and demonstrated previous efficacy as a PAFI [20]. In this retrospective case series of 25 patients, OFM was able to achieve healing and maintain closure in 76% (n = 19) of cases at 12-weeks with a median healing time of 4.5 weeks with a median single application (Table 4). Using Park's classification, the majority of the PFs were transsphincteric in nature (72%) with a mean depth of 3.3 ± 1.6 cm (Table 3). Only one patient presented with a recurrence at 12-weeks. At 6 weeks following index PAFI, the patient presented with intermittent sanguinous drainage via a small unhealed opening and was treated with a course of antibiotics. Upon further follow-up, a recurrence was noted and a second OFM PAFI was placed 4 months after the index surgery. Approximately 5.5 weeks following the second procedure, the defect healed without further complication. At last follow-up, 21 out of 25 PFs (84%) remained healed.

Table 4
Post-operative Clinical Outcomes

Characteristic	Value
Post-operative pain, % (n)	20.0% (5)
Time to heal (weeks), median (IQR), [mean ± SD], (n)	4.5 (4.0–6.0), [6.1 ± 5.0], (22)
Outcome at 12 Weeks	
Remains healed, % (n)	76.0% (19)
Not healed, % (n)	12.0% (3)
Not reported, % (n)	8.0% (2)
Recurrence, % (n)	4.0% (1)
Maximum follow-up duration (weeks), median (IQR), [mean ± SD], (n)	25.0 (15.5–29.5), [24.4 ± 14.3], (25)
Outcome at last follow-up visit	
Remains healed, % (n)	84.0% (21)
Not healed, % (n)	16.0% (4)
Recurrence, % (n)	0.0% (0)
Abbreviations: n, sample size; SD, standard deviation of the mean; IQR, interquartile range	

The study was comprised predominately of PFs secondary to cryptoglandular infection (92%) and represent chronic, highly inflammatory defects. The chronic nature of the PF defects was further evidenced by over half of patients having prior seton use for a median duration of 35 weeks. The proven ability of OFM to function in hostile, inflammatory microenvironments and modulate wound proteases has been well documented in both preclinical [22, 30] and clinical studies [26, 27, 31]. It is postulated that the success of OFM observed in this study is in part due to the ability for OFM to function and retain bioactivity in chronically inflammatory PF tissue. Additionally, OFM has demonstrated angiogenic activity [25]. Due to the high vascularity of the perianal region, OFM may be particularly well suited to take advantage and promote healthy tissue formation in this environment. Interestingly, OFM has shown the ability to recruit mesenchymal stem cells (MSCs) [24] and retain growth factors (KGF, BMP, PDGF, VEGF) and chemokines that promote tissue growth [21]. Using the same principle, the use of stem cell therapy is an increasingly common treatment strategy for PFs [14] with demonstrated instances of success, particularly in PFs associated with Crohn's disease [32]. We hypothesize that OFM may be acting as not only a classic anal fistula plug but may additionally be acting as a multimodal therapy due to recruitment of progenitor cells. Furthermore, OFM was selected as a PAFI device due to the ease of use and customizable operative sizing such that it is unique to the anatomy of each defect during surgery.

LIFT procedures are being increasingly reported in the literature and adopted in clinical practice. Studies have reported varying degrees of recurrence ranging from a 60% recurrence rate [33] to as low 16.7% [34] and 12.5% [35]. These reported recurrence rates are notably higher than our observed recurrence rate of 4% at 12 weeks and 0% at final follow-up of median 25.0 weeks. However, it is worth noting the low reported rates of incontinence with the LIFT technique in these studies compared to other invasive methods of surgical intervention. Our current study reports no instances of incontinence in the 25 patients analyzed. A study by Zhao et al reports a much-reduced recurrence rate when LIFT is used in combination with an anal fistula plug with a 96.2% success rate [2]. Similar to the LIFT procedure, studies highlighting anal fistula plugs demonstrate varying degrees of success. Jayne et al highlights data comparing anal fistula plugs to other common techniques and reports healing incidence at 12-months as follows: fistula plug 55%, cutting seton 64%, fistulotomy 75%, advancement flap 53%, and LIFT technique 42% [10]. Chen et al reports outcomes using decellularized small intestine submucosa (SIS)-based anal fistula pugs of two different products (porcine and synthetic) healing rates at 6-months of 92.0% and 89.2% with recurrence rates of 2.4% in both groups [36]. Long-term follow-up data at a median 8-years was reported by Tao et al and found a 56% healing rate for anal fistula plugs, which emphasizes the variability in reported healing ranges [37]. A study using a single application of porcine urinary bladder matrix in 19 patients with PFs reported a 79% closure rate at a mean 17 day days with a mean 7 month follow-up [19]. However, another study using acellular dermal matrices reports a 59.1% success rate at median 42 months follow-up [38] These data suggest that although dermal matrices and implants show promise, additional studies are needed to further assess efficacy at long-term follow-up and in a greater number of patients. Recent advances in MSC carrying matrices show promise in PF secondary to Chron's disease but, like other biological matrices, require further research [39, 40].

There are several limitations to this study. These are retrospective data collected on a relatively small patient sample. Prospective clinical trials with a larger cohort followed for a longer duration will be required to justify widespread clinical adoption of OFM-based PAFI for PF treatment. Future work can include a comparative arm, further cost-analysis, and a longer follow-up period to monitor for recurrence. OFM-based PAFI studies can additionally include the combination of additional surgical techniques that are often used in combination with plugs and implants.

Conclusion

In conclusion, the promising results of this retrospective case series builds up on previously published pilot study data and further suggests that an OFM implant (PAFI) may be a clinically successful and minimally invasive treatment option for the treatment of PF.

Declarations

Acknowledgments

The authors wish to acknowledge Andrew W. Ross, DO (Medical Writer, Aroa Biosurgery Limited) for assistance in the preparation of this manuscript. We additionally thank the clinical and surgical staff at Nuvance Health Vassar Brothers Medical Center for their efforts and excellent patient care.

Conflict of Interest Statement

JC and PK are consultants for Aroa Biosurgery Limited.

References

1. Garcia-Botello S, Garces-Albir M, Espi-Macias A, Moro-Valdezate D, Pla-Marti V, Martin-Arevalo J, Ortega-Serrano J (2021) Sphincter damage during fistulotomy for perianal fistulae and its relationship with faecal incontinence. Langenbecks Arch Surg 406(7):2497-2505. https://10.1007/s00423-021-02307-5
2. Zhao B, Wang Z, Han J, Zheng Y, Cui J, Yu S (2019) Long-term outcomes of ligation of the inter-sphincteric fistula tract plus bioprosthetic anal fistula plug (lift-plug) in the treatment of trans-sphincteric perianal fistula. Med Sci Monit 25:1350-1354. https://10.12659/MSM.914925
3. Tsai L, McCurdy JD, Ma C, Jairath V, Singh S (2022) Epidemiology and natural history of perianal crohn's disease: A systematic review and meta-analysis of population-based cohorts. Inflamm Bowel Dis 28(10):1477-1484. https://10.1093/ibd/izab287
4. Choi YS, Kim DS, Lee DH, Lee JB, Lee EJ, Lee SD, Song KH, Jung HJ (2018) Clinical characteristics and incidence of perianal diseases in patients with ulcerative colitis. Ann Coloproctol 34(3):138-143. https://10.3393/ac.2017.06.08
5. Sica GS, Di Carlo S, Tema G, Montagnese F, Del Vecchio Blanco G, Fiaschetti V, Maggi G, Biancone L (2014) Treatment of peri-anal fistula in crohn's disease. World J Gastroenterol 20(37):13205-10. https://10.3748/wjg.v20.i37.13205
6. Agrawal M and Jess T (2022) Implications of the changing epidemiology of inflammatory bowel disease in a changing world. United European Gastroenterol J 10(10):1113-1120. https://10.1002/ueg2.12317
7. Bhat S, Xu W, Varghese C, Dubey N, Wells CI, Harmston C, O'Grady G, Bissett IP, Lin AY (2023) Efficacy of different surgical treatments for management of anal fistula: A network meta-analysis. Tech Coloproctol 27(10):827-845. https://10.1007/s10151-023-02845-8
8. An Y, Gao J, Xu J, Qi W, Wang L, Tian M (2024) Efficacy and safety of 13 surgical techniques for the treatment of complex anal fistula, non-crohn caf: A systematic review and network meta-analysis. Int J Surg 110(1):441-452. https://10.1097/JS9.0000000000000776
9. Cheung XC, Fahey T, Rogers AC, Pemberton JH, Kavanagh DO (2021) Surgical management of idiopathic perianal fistulas: A systematic review and meta-analysis. Dig Surg 38(2):104-119. https://10.1159/000512652

10. Jayne DG, Scholefield J, Tolan D, Gray R, Edlin R, Hulme CT, Sutton AJ, Handley K, Hewitt CA, Kaur M, Magill L (2019) Anal fistula plug versus surgeon's preference for surgery for trans-sphincteric anal fistula: The fiat rct. Health Technol Assess 23(21):1-76. https://10.3310/hta23210
11. Tian Z, Li YL, Nan SJ, Xiu WC, Wang YQ (2022) Video-assisted anal fistula treatment for complex anorectal fistulas in adults: A systematic review and meta-analysis. Tech Coloproctol 26(10):783-795. https://10.1007/s10151-022-02614-z
12. Nordholm-Carstensen A, Perregaard H, Hagen KB, Krarup PM (2021) Fistula laser closure (filac) for fistula-in-ano-yet another technique with 50% healing rates? Int J Colorectal Dis 36(9):1831-1837. https://10.1007/s00384-021-03932-8
13. Elfeki H, Shalaby M, Emile SH, Sakr A, Mikael M, Lundby L (2020) A systematic review and meta-analysis of the safety and efficacy of fistula laser closure. Tech Coloproctol 24(4):265-274. https://10.1007/s10151-020-02165-1
14. Wang H, Jiang HY, Zhang YX, Jin HY, Fei BY, Jiang JL (2023) Mesenchymal stem cells transplantation for perianal fistulas: A systematic review and meta-analysis of clinical trials. Stem Cell Res Ther 14(1):103. https://10.1186/s13287-023-03331-6
15. Park MY, Yoon YS, Kim HE, Lee JL, Park IJ, Lim SB, Yu CS, Kim JC (2021) Surgical options for perianal fistula in patients with crohn's disease: A comparison of seton placement, fistulotomy, and stem cell therapy. Asian J Surg 44(11):1383-1388. https://10.1016/j.asjsur.2021.03.013
16. Bondi J, Avdagic J, Karlbom U, Hallbook O, Kalman D, Saltyte Benth J, Naimy N, Oresland T (2017) Randomized clinical trial comparing collagen plug and advancement flap for trans-sphincteric anal fistula. Br J Surg 104(9):1160-1166. https://10.1002/bjs.10549
17. Tao Y, Zheng Y, Han JG, Wang ZJ, Cui JJ, Zhao BC, Yang XQ (2021) Effects of an anal fistula plug on anal function after surgery for treatment of a trans-sphincteric anal fistula. Langenbecks Arch Surg 406(3):855-861. https://10.1007/s00423-020-02024-5
18. Kockerling F, Alam NN, Narang SK, Daniels IR, Smart NJ (2015) Treatment of fistula-in-ano with fistula plug - a review under special consideration of the technique. Front Surg 2:55. https://10.3389/fsurg.2015.00055
19. Iorio T and Blumberg D (2015) Short-term results of treating primary and recurrent anal fistulas with a novel extracellular matrix derived from porcine urinary bladder. Am Surg 81(5):498-502.
20. Hsu A, Schlidt K, D'Adamo CR, Bosque BA, Dowling SG, Wolf JH (2023) Surgical management of perianal fistula using an ovine forestomach matrix implant. Tech Coloproctol 27(9):769-774. https://10.1007/s10151-023-02809-y
21. Lun S, Irvine SM, Johnson KD, Fisher NJ, Floden EW, Negron L, Dempsey SG, McLaughlin RJ, Vasudevamurthy M, Ward BR, May BC (2010) A functional extracellular matrix biomaterial derived from ovine forestomach. Biomaterials 31(16):4517-29. https://10.1016/j.biomaterials.2010.02.025
22. Negron L, Lun S, May BCH (2012) Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 11(4):392-397.

23. Bohn G, Liden B, Schultz G, Yang Q, Gibson DJ (2016) Ovine-based collagen matrix dressing: Next-generation collagen dressing for wound care. Adv Wound Care (New Rochelle) 5(1):1-10. https://10.1089/wound.2015.0660
24. Dempsey SG, Miller CH, Schueler J, Veale RWF, Day DJ, May BCH (2020) A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo. PLoS One 15(7):e0235784. https://10.1371/journal.pone.0235784
25. Irvine SM, Cayzer J, Todd EM, Lun S, Floden EW, Negron L, Fisher JN, Dempsey SG, Alexander A, Hill MC, O'Rouke A, Gunningham SP, Knight C, Davis PF, Ward BR, May BCH (2011) Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. Biomaterials 32(27):6351-61. https://l10.1016/j.biomaterials.2011.05.040
26. Chaffin AE and Buckley MC (2020) Extracellular matrix graft for the surgical management of hurley stage iii hidradenitis suppurativa: A pilot case series. J Wound Care 29(11):624-630. https://10.12968/jowc.2020.29.11.624
27. Chaffin AE, Dowling SG, Kosyk MS, Bosque BA (2021) Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: A case series. J Wound Care 30(Sup7):S28-S34. https://10.12968/jowc.2021.30.Sup7.S28
28. DeNoto G, Ceppa EP, Pacella SJ, Sawyer M, Slayden G, Takata M, Tuma G, Yunis J (2021) A prospective, single arm, multi-center study evaluating the clinical outcomes of ventral hernias treated with ovitex® 1s permanent reinforced tissue matrix: The bravo study 12-month analysis. J Clin Med 10(21):4998. https://https://doi.org/10.3390/jcm10214998
29. Timmer AS, Claessen JJM, Brouwer de Koning IM, Haenen SM, Belt EJT, Bastiaansen A, Verdaasdonk EGG, Wolffenbuttel CP, Schreurs WH, Draaisma WA, Boermeester MA (2022) Clinical outcomes of open abdominal wall reconstruction with the use of a polypropylene reinforced tissue matrix: A multicenter retrospective study. Hernia 26(5):1241-1250. https://10.1007/s10029-022-02604-y
30. Overbeck N, Nagvajara GM, Ferzoco S, May BCH, Beierschmitt A, Qi S (2020) In-vivo evaluation of a reinforced ovine biologic: A comparative study to available hernia mesh repair materials. Hernia 24(6):1293-1306. https://10.1007/s10029-019-02119-z
31. Desvigne MN, Bauer K, Holifield K, Day K, Gilmore D, Wardman AL (2020) Case report: Surgical closure of chronic soft tissue defects using extracellular matrix graft augmented tissue flaps. Front Surg 7:559450. https://10.3389/fsurg.2020.559450
32. Cao Y, Su Q, Zhang B, Shen F, Li S (2021) Efficacy of stem cells therapy for crohn's fistula: A meta-analysis and systematic review. Stem Cell Res Ther 12(1):32. https://10.1186/s13287-020-02095-7
33. Vander Mijnsbrugge GJH, Felt-Bersma RJF, Ho DKF, Molenaar CBH (2019) Perianal fistulas and the lift procedure: Results, predictive factors for success, and long-term results with subsequent treatment. Tech Coloproctol 23(7):639-647. https://10.1007/s10151-019-02023-9
34. Rydzek M, Ciesielski P, Diuwe P (2021) The results of high-position anal fistula treatment using the lift (ligation of intersphincteric fistula tract) procedure. A retrospective, single-center study. Pol

Przegl Chir 93(4):41-45. https://10.5604/01.3001.0014.8769

35. Celayir MF, Bozkurt E, Aygun N, Mihmanli M (2020) Complex anal fistula: Long-term results of modified ligation of intersphincteric fistula tract=lift. Sisli Etfal Hastan Tip Bul 54(3):297-301. https://10.14744/SEMB.2020.89106
36. Chen ZW, Zheng Y, Zhao R, Wang ZJ (2022) Treatment of anal fistula using a decellularized porcine small intestinal submucosa plug: A non-inferiority trial. Medicine (Baltimore) 101(29):e29110. https://10.1097/MD.0000000000029110
37. Tao Y, Zheng Y, Han JG, Wang ZJ, Cui JJ, Zhao BC, Yang XQ (2020) Long-term clinical results of use of an anal fistula plug for treatment of low trans-sphincteric anal fistulas. Med Sci Monit 26:e928181. https://10.12659/MSM.928181
38. Gomez-Jurado MJ, Marti-Gallostra M, Pellino G, Galvez A, Kreisler E, Biondo S, Espin-Basany E (2022) Long-term outcomes of an acellular dermal matrix for the treatment of complex cryptoglandular anal fistula: A pilot study. Tech Coloproctol 26(6):453-459. https://10.1007/s10151-022-02593-1
39. Dozois EJ, Lightner AL, Dietz AB, Fletcher JG, Lee YS, Friton JJ, Faubion WA (2023) Durable response in patients with refractory fistulizing perianal crohn's disease using autologous mesenchymal stem cells on a dissolvable matrix: Results from the phase i stem cell on matrix plug trial. Dis Colon Rectum 66(2):243-252. https://10.1097/DCR.0000000000002579
40. Dietz AB, Dozois EJ, Fletcher JG, Butler GW, Radel D, Lightner AL, Dave M, Friton J, Nair A, Camilleri ET, Dudakovic A, van Wijnen AJ, Faubion WA (2017) Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with crohn's disease. Gastroenterology 153(1):59-62 e2. https://10.1053/j.gastro.2017.04.001