



Efficacy of autologous fat graft injection in the treatment of anovaginal fistulas

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Abstract

Background Injection of autologous fat is an established method within plastic surgery for soft tissue augmentation. The aim of the present study was to determine whether transperineal fat graft injection could promote healing of anovaginal fistulas.

Methods The procedures were performed at the University Hospital of North Norway, Tromsø, Norway, and at Aarhus University Hospital, Aarhus, Denmark, between May 2009 and September 2016. After abdominal liposuction, fat was injected around the fistula tract that was finally transected percutaneously with a sharp cannula and fat injected between the cut parts. The internal opening was closed with a suture. Patients had a minimum follow-up of 6 months after last fat graft injection.

Results Twenty-seven women underwent 48 procedures. The cause of fistula was obstetric ($n = 9$), abscess ($n = 9$), Crohn's disease ($n = 7$), radiation for anal cancer ($n = 1$) and endoscopic surgery after radiation for rectal cancer ($n = 1$). The mean amount of injected fat was 73 ml (SD $\pm$ 20 ml), and operating time was 63 min (SD $\pm$ 21 min). At median follow-up of 20 months (range 6–87 months) after the last injection, fistulas were healed in 21 women (77%), in 8 women after just one procedure. Healing was achieved in 6 of 7 women (86%) with Crohn's disease and in both women who had undergone radiation therapy. One woman developed an abscess and additional trans-sphincteric fistula 8 weeks after injection.

Conclusions Fat graft injection for anovaginal fistulas is effective and safe.

Keywords Anovaginal · Rectovaginal · Fistula · Crohn's disease · Fat · Transplantation

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Introduction

An anovaginal fistula is an epithelized tract between the anal canal and the vagina, resulting in passage of stool, mucus or gas into the vagina. In an anovaginal fistula, the inner opening is located within the anal canal in contrast to a rectovaginal fistula where the inner opening is found proximal to the anal canal [1].

Anovaginal fistulas are most commonly caused by obstetric injuries, followed by Crohn's disease, pelvic surgery for benign or malignant diseases, cryptoglandular abscess, neoplasms and radiation therapy [1, 2]. The treatment of these fistulas represents a challenge, as recurrence is common. Healing after less invasive procedures like fistula plug and metal clip application is disappointing with success rates between 20 and 45% [3]. The reported healing rate after more invasive techniques like advancement flaps, Martius flaps, biological mesh implants, transperineal fistulectomy with sphincteroplasty, or transposition of the gracilis muscle is 60–100% in various series [3–5], but these procedures are associated with morbidity such as pain in the perineum or at

the donor site, impairment of sexual life and incontinence [6, 7]. Many women have to undergo several procedures in order to achieve fistula healing, with each procedure carrying its own risks of postoperative complications and deterioration of functional outcome. Furthermore, a diverting stoma is frequently needed during the course of the treatment [8].

Soft tissue augmentation with autologous fat grafting after liposuction is an established method within plastic surgery. After standardization of the procedure by Coleman [9], the method has been used successfully for soft tissue augmentation in a variety of disorders [10]. The first pilot study by de Weerd et al. [11] of autologous fat graft injection in 6 patients with recalcitrant anovaginal fistulas reported a healing rate of 67%. Following the treatment of these first patients, the procedure was established as a treatment option for anovaginal fistulas at the University Hospital of North Norway in 2013 and at the Aarhus University Hospital 1 year later. The aim of this study was to report the results for all women treated with autologous fat graft injection for anovaginal fistulas at the two institutions with a minimum follow-up of 6 months after last injection. The primary endpoint was the clinical healing rate. Secondary endpoints were postoperative complications necessitating unplanned reoperation or rehospitalisation, and stoma reversal rate.

Ethical considerations

Informed consent was obtained from all patients before treatment. As the procedure already was well established for a variety of conditions and the study classified as a quality project, approval from the local committees of research ethics was not needed according to Norwegian and Danish regulations. None of the authors had any conflict of interests related to the study.

Patients and method

All women with anovaginal fistulas were eligible for inclusion, but women with a complete anal sphincter defect and faecal incontinence were offered fistulectomy and closure with sphincteroplasty if not already performed. The present study also included the 6 women from the pilot study [11]. Before inclusion, a complete medical history was obtained. Clinical investigation including vaginal inspection and proctoscopy with careful probing and classification of the fistula was undertaken. In case of sepsis, a seton was placed for at least 6 weeks prior to treatment. Magnetic resonance imaging (MRI) was not performed routinely prior to treatment, but used in case of Crohn's disease to exclude the presence of additional fistula tracts. Smoking or nicotine substitution of any kind had to be ceased at least 8 weeks prior to fat injection.

The procedure was performed with the patient in the lithotomy position under general anaesthesia. Prophylactic antibiotics, 1.5 g Cefalotin and 1.5 g metronidazole, were administered intravenously. A mixture of 400 mg of lidocaine, 1 mg of adrenaline and 50 mmol of sodium bicarbonate was added to 1000 ml of Ringer's solution, and 300 ml of this mixture was injected into the subcutaneous fat of the lower abdomen. Thereafter, approximately 150 ml of fat suspension was harvested by manual liposuction. The suspension was centrifuged for 2 min at 3000 rpm before the infranatant was removed. From 2014, the spinning was reduced to 1000 rpm, as more cautious spinning might improve the viability of the fat graft [12, 13].

The fistula tract was carefully prepared removing the epithelium and granulation tissue with a curette, and a thin catheter was placed through the fistula tract to facilitate orientation during the procedure. Two small incisions were made at each side of the perineal midline, and fat graft was injected transperineally around the fistula tract using a 10-ml syringe and a blunt Coleman® 14-G fat injection cannula (Fig. 1). The fat was injected around the fistula tract creating a “doughnut” appearance. Care was taken to inject the fat at different levels and using multiple passes with only 2–3 ml injected at each pass, in order to facilitate optimal conditions for survival of the transplant [14]. Finally, the fistula tract was cut transversely using a sharp Coleman® fat injection cannula using the catheter placed in the fistula tract as guidance. During transection, fat was protruding from the internal and external opening. Efforts were made to transect the fistula tract completely. The various steps are shown schematically in Fig. 2. The

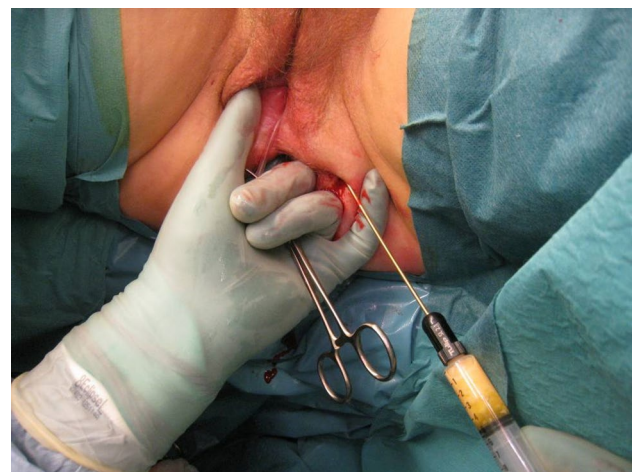
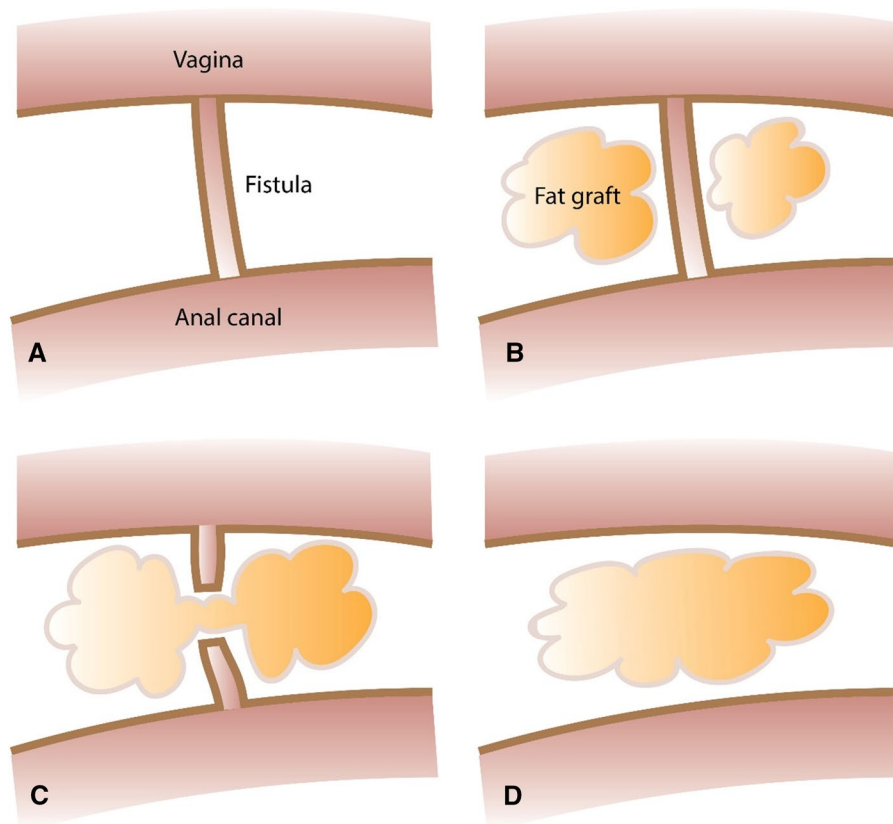


Fig. 1 A fat graft injected transperineally around the fistula tract using a 10-ml syringe and a blunt Coleman® 14-G fat injection cannula. A catheter has been placed through the anovaginal fistula, and the two catheter ends are fixed with a peang. The fat is injected transperineally using a 10-ml syringe and a blunt Coleman® 14-G fat injection cannula

Fig. 2 The various steps of the procedure shown schematically. **a** Anovaginal fistula, **b** fat graft injected around the fistula, **c** fistula transected transversely, **d** viable fat graft in the area where the fistula was located



catheter was removed, and the fistula opening in the vagina was closed with absorbable sutures (4-0 Vicryl Rapid®, Ethicon) without closing the internal opening in the anal canal. From 2014, this was altered according to a mutual protocol, and the internal opening in the anal canal was closed with glycolide/lactide copolymer absorbable suture (Polysorb® 3-0, Medtronic) without closing the opening in the vagina. Ciprofloxacin 500 mg $\times$ 2 was given orally for 5 days and 1000 mg ascorbic acid daily for 6 weeks due to its multifaceted positive effect on the mesenchymal stem cells present in the lipoaspirate [15]. Postoperative pain was treated with paracetamol and ibuprofen. A second fat injection procedure was scheduled after 6–8 weeks if healing was not obtained after the first treatment. The patients were instructed to contact the hospital if experiencing increased pain, fever or discharge of pus from the area, or if other complications were suspected. A follow-up of 6 weeks after a second injection was performed in addition to a follow-up after 6 months. A fistula was considered healed if the woman had no symptoms of discharge of faeces or gas from the vagina, and no fistula opening in the anal canal or posterior vaginal wall evident at clinical investigation. Data were analysed using IBM SPSS Statistics version 24. Numeric variables were presented as mean or median when appropriate, with standard deviation (SD) or interquartile range (IQR) in brackets. Tests

for significance were not performed because of limited number of patients and the inhomogeneous patient group.

Results

From May 2009 to September 2016, a total of 27 women (14 in Tromsø and 13 in Aarhus) were treated with autologous fat injection for anovaginal fistulas and with a follow-up of 6 months or more after last injection. Mean age at the time of operation was 42 years (standard deviation (SD) $\pm$ 10 years.). A total of 21 women (77%) had undergone at least 1 prior surgical attempt of fistula repair, and 13 women (48%) had undergone 2 or more surgical fistula procedures prior to fat injection. The various procedures are shown in Table 1. The aetiology was obstetric in 9 cases (33%) and Crohn's disease on 7 cases (26%). Patient characteristics are listed in Table 2. A total of 48 fat injection procedures were performed, with a mean of 73 ml fat (SD $\pm$ 20 ml) injected at each procedure. Mean operating time was 63 min (SD $\pm$ 21 min).

After a median follow-up duration of 20 months (interquartile range (IQR) 14–38 months), the fistula was healed in 21 women (77%). In 8 women (30%), 1 of whom had Crohn's disease, the fistula healed after 1 treatment. The healing rate among patients treated between 2009 and

Table 1 Previous fistula procedures

Procedures prior to fat injection	Procedures (n)	Patients (n) ^a
Plug	10	8
Ligation of intersphincteric fistula tract (LIFT)	4	4
Advancement flap	11	8
Mesh	1	1
Fistulectomy with sphincteroplasty	4	3
Fasciocutaneous graft	3	2
Fistulectomy	1	1
Posterior colporrhaphy	1	1

^aA total of 21 patients had undergone previous attempts at fistula closure prior to fat graft injection. Some of these had undergone multiple procedures

Table 2 Patient characteristics and operative data related to outcome

	All patients (n = 27)	Healed (n = 21)	Not healed (n = 6)
Age, years (mean ± SD)	41.7 ± 10.2	42.4 ± 9.6	39.3 ± 12.4
Body mass index, kg/m ² (mean ± SD)	28.2 ± 5.2	28.6 ± 4.9	26.7 ± 5.7
Aetiology (%)			
Obstetric	9	8 (89)	1 (11)
Abscess	9	5 (56)	4 (44)
Crohn's disease	7	6 (86)	1 (14)
Radiotherapy for anal cancer	1	1 (100)	0
Transanal endoscopic resection	1	1 (100)	0
Fistula repairs prior to fat injection (mean ± SD)	1.7 ± 1.3	1.9 ± 1.3	1.0 ± 0.9
Injected fat per procedure, ml (mean ± SD)	73 ± 20	76 ± 20	65 ± 18
Covering stoma (%)	10/27 (37)	8/21 (38)	2/6 (33)
Stoma at latest follow-up	3	2	1

2013 and among patients treated from 2014 and forward was 6/7 (86%) and 15/20 (75%), respectively. One patient who achieved healing of a fistula following radiotherapy for anal cancer died of reasons unrelated to the cancer or fistula treatment 11 months after the last fat injection. One woman with a healed fistula at 6 and 12 weeks following a single injection experienced a recurrence after 24 weeks. She had another 2 injection procedures 6 months after the recurrence, and the fistula was still healed at follow-up of 6 months after the last injection.

Fistula healing was achieved in 6 of 7 women (86%) with Crohn's disease with a median follow-up of 25 months (IQR 9–42) after the last injection. Three of the 6 women with healed Crohn's fistula were not receiving biological medication at latest follow-up. One woman with Crohn's disease had a recurrence 24 months after healing and had 2 additional procedures and the fistula remained healed at latest follow-up of 23 months after the last injection. Another woman with Crohn's disease, reported as a failure in the first series [11] due to clinical suspicion of recurrence after 23 months, had no symptoms nor signs of recurrence on

MRI and anovaginal investigations after a follow-up of 39 months.

Ten women (37%) had a stoma before treatment with fat injection compared to 3 (11%) at latest follow-up; 1 received a colostomy due to lack of healing, and another with fistula following local excision of the remaining scar after an irradiated distal rectal cancer with complete clinical response was satisfied with her colostomy although repeated clinical investigations and MRI as part of the oncological follow-up confirmed that the fistula was healed. A third woman was still awaiting stoma reversal 10 months after the fistula was healed.

One woman (4%) in whom the fistula was healed 6 weeks after a single injection was readmitted 8 weeks after the injection with a perianal abscess resulting in a trans-sphincteric fistula in addition to recurrence of the anovaginal fistula. She underwent abscess drainage followed by a successful ligation of the intersphincteric fistula tract (LIFT) procedure of the trans-sphincteric fistula and is scheduled for another fat injection. No other complications necessitating reoperation or rehospitalisation were observed.

Discussion

In the present study, over 75% of women treated with autologous fat injection for anovaginal fistulas had no signs of fistula after a median follow-up duration of more than 1.5 years. Five surgeons at 2 different hospitals performed the procedures, indicating that the method is feasible and the results are reproducible. Our results confirm the findings from the first pilot study including 6 patients with recalcitrant anovaginal fistulas treated with this method [11].

Although autologous fat injection has become an established and well-documented method for soft tissue augmentation in a variety of disorders, it has just recently begun to be used for perineal fistulas. In 2013, de Weerd et al. [16] reported a case where the method was successfully used to treat a patient with a rectourethral fistula after prostatectomy, and in 2015, the same group published a pilot study where the method had been applied on anovaginal fistulas [11]. There are several reasons why injection of autologous fat could promote fistula healing. In addition to adipocytes, the lipoaspirate contains preadipocytes, mesenchymal stem cells, endothelial cells, fibroblasts and hematopoietic-lineage cells which possess regenerative properties promoting neoangiogenesis, wound healing and tissue growth [17, 18]. Furthermore, the mesenchymal stem cells produce a variety of substances with significant anti-inflammatory and immunomodulatory properties in the target area [19]. For this reason, adipose-derived mesenchymal stem cells have been cultured and used in the treatment of both Crohn's and non-Crohn's fistulas, with reported healing rates between 50 and 70% [20–22]. Local injections of cultured mesenchymal stem cells have also been used in the treatment of rectovaginal Crohn's fistulas, and Garcia-Arranz et al. [23] achieved fistula healing at 1-year follow-up in 3 out of 5 women. In contrast to treatment with cultured stem cells, autologous fat graft injection is less expensive and easily performed as a one-step procedure. Furthermore, the mesenchymal stem cells represent just a small fraction of the lipoaspirate, and injections of autologous fat supply the scar tissue with viable adipocytes and preadipocytes which survive in the recipient area and thereby promote healing [14].

Interestingly, in the present study autologous fat injection was very effective in women with anovaginal Crohn's fistulas, with a healing rate exceeding 80%. In a series by Athanasiadis et al. [7], reporting the outcome of 56 various surgical procedures in 37 women with rectovaginal fistulas and Crohn's disease, the overall healing rate was 73%. Although several studies report similar initial healing rates [8, 24], the reported long-term recurrence rate for anovaginal Crohn's fistulas is 10–54% [7, 25–27]. In

our subgroup of women with Crohn's disease, 1 woman experienced recurrence 2 years after the treatment. She was successfully treated with another 2 injections with no recurrence at follow-up of 2 years later. Further studies are needed to determine the long-term success rate following autologous fat injection for anovaginal fistulas in the presence of Crohn's disease, but the results so far are promising.

Postoperative complications necessitating rehospitalisation or reoperation occurred in only 1 woman who developed a perianal abscess and a second fistula in addition to the anovaginal fistula. Fat necrosis at the recipient site is a known complication of autologous fat injections in general [10]. To reduce the risk of necrosis, an essential step of the procedure is to inject the fat in a fan shaped fashion into separate tunnels to ensure optimal conditions for revascularisation [14]. Nevertheless, as the anovaginal fistula tract is cut at the end of the procedure, faecal contamination of the transplanted fat is likely to occur, especially when the fistula opening in the anal canal is not closed like in the first part of this series. Although antibiotics were given during and after the procedures, we expected infectious complications to occur more frequently. The low incidence of infectious complications can be explained by the strong anti-inflammatory properties of the mesenchymal stem cells found in the injected lipoaspirate [19]. Moreover, the complication rate following autologous fat injection in our series is not higher than after the conventional procedures for these fistulas [8].

A protecting stoma was present in more than a third of the women prior to fat injection. The stomas had been established prior to other fistula procedures in all cases. There was no apparent difference in healing rate in women with or without a protecting stoma (Table 2). This is in accordance with other studies [8, 27]. The stoma reversal rate in our study was 80%, and the remaining 20% was due to 1 patient's preference and 1 patient still being on the waiting list for stoma reversal. In a large series by Byrnes et al. [8] where success was defined as the absence of both symptoms and stoma at least 3 months after the last procedure, stomas were reversed in 18 of 44 women (42%) and 38% of the women met the success criteria as defined above. Using this definition, 70% of the women could be regarded as successfully treated in our study.

The present study has several limitations. Although data have been recorded prospectively, the design is retrospective. The included number of patients is also limited. Furthermore, functional data regarding continence status, defecation disorders, sexual life and perianal problems like discomfort or pain are lacking. Functional outcome is an important aspect of fistula surgery and should be included in future studies of fat injections for perineal fistulas. Another issue is that the term "rectovaginal fistula" is commonly used also for anovaginal fistulas. This is exemplified by the published

pilot of the first 6 women treated with autologous fat injections, where the fistulas were described as rectovaginal although being anatomically anovaginal in all cases [11]. True rectovaginal fistulas are less common, and the correct characterization would be anovaginal in most cases [1]. This lack of uniform definition must be kept in mind when comparing results from different studies. While true rectovaginal fistulas are best treated by transabdominal procedures, the low fistulas should be treated from below with perineal, transvaginal or transanal procedures [6, 8].

Conclusions

Autologous fat graft injection is effective to treat anovaginal fistulas regardless of aetiology and previous surgical attempts at fistula closure. The complication rate is low, and the procedure does not preclude more comprehensive methods if fistula healing is not obtained. Further studies are warranted to assess functional outcome and long-term results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Approval from local committees of research ethics was not needed according to Norwegian and Danish regulations.

Informed consent The patients was thoroughly informed about the procedure and possible risk factors, and all patients gave their informed consent prior to surgery.

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