**Volume 22 Number 3**
**March 2016**

**Case presentation**

# Innovative use of chemodenervation in the treatment of postoperative genital hyperhidrosis-like symptoms

**Kelly R Stiegel BS, Eman Bahrani BA, Ramsey F Markus MD**

**Dermatology Online Journal 22 (3): 15**

**Department of Dermatology, Baylor College of Medicine, Houston, TX 77030**

**Correspondence:**

Ramsey F. Markus, MD
Jamail Specialty Care Center
1977 Butler Blvd., Suite E6.200
Houston, TX 77030
rmarkus@bcm.edu
(713) 798-6925

## Abstract

Postoperative complications present in many forms and can cause great morbidity and even mortality in patients who experience them. Frey syndrome is an example of a postoperative complication in which aberrant nerve regeneration following parotidectomy leads to hyperhidrosis induced by gustatory stimuli. We present a unique but similar case of aberrant nerve regeneration and resulting hypersecretion that emerged 6-7 months following perineoplasty and labial reduction for lichen sclerosus in a 53-year-old woman. An exhaustive investigation ruled out genitourinary causes of her symptoms. Pads, tampons, and surgical procedures provided no relief. We propose that the mechanism of her excessive watery secretions is similar to that which causes Frey syndrome: iatrogenic damage to nerves that aberrantly regenerate to innervate local structures involved in secretory control. The parallels between our patient's condition and Frey syndrome are evident in the duration between surgery and onset of symptoms and the response to treatment with onabotulinum toxin, highlighting a shared cholinergic pathway. Onabotulinum injections are well tolerated by patients with localized hyperhidrosis and symptom control typically lasts several months. In this manuscript we present a novel mode of delivery of onabotulinum toxin topically to a mucosal region. With these treatments, the patient's hyperhidrosis-like symptoms remain well controlled for 3-4 months, at which point she returns to clinic for treatment. The patient did not experience symptomatic relief until this unique treatment plan was initiated. Her case illustrates the need for further understanding of recalcitrant postoperative complications involving local structures controlling liquid secretion, such as sweat glands and vascular plexuses.

**Keywords: Botulinum Toxins, Type A; Hyperhidrosis; Lichen Sclerosus et Atrophicus; Sweating, Gustatory**

## Introduction

Hyperhidrosis is a condition of excessive perspiration categorized as either primary or secondary [1]. Primary hyperhidrosis is an idiopathic disorder of superfluous, bilateral sweat production, associated with hyperactivity of the sympathetic nervous system. Secondary hyperhidrosis is related to an underlying infectious, endocrine, neoplastic, neurologic, spinal cord, or psychiatric condition [2]. Available treatments for these debilitating conditions include topical medications, iontophoresis, oral anticholinergics, botulinum toxin injections, and surgery. Botulinum toxin binds to presynaptic recognition sites on cholinergic nerve terminals, decreasing the release of acetylcholine, thereby reducing the nerve transduction signal and eccrine gland stimulation [3].

Labioplasty and perineoplasty are gynecologic surgeries involving incision of heavily innervated and vascularized epithelium and mucosae containing myriad structures involved in sweating and lubrication, such as Bartholin's glands, eccrine sweat glands, apocrine sweat glands, and rich superficial vascular plexuses [4]. Neuronal structures of the lower vagina and vaginoperineal regions include branches of the pudendal nerve terminating as the deep perineal and posterior labial nerves. Pudendal nerve branches provide both autonomic and somatic innervation to structures in these regions using acetylcholine, among other neurotransmitters [5, 6].

## Case synopsis

A 53-year-old woman with past history of lichen sclerosus and interstitial cystitis, perineoplasty with labial reduction, and total hysterectomy, presented to the dermatology clinic with a 5-year history of copious watery discharge in the genital region. The patient reported normal vaginal moisture before February 2008, at which time she underwent a perineoplasty and bilateral labial reduction for a circular stricture around the introitus and hypertrophy of the labia minora for the treatment of chronic lichen sclerosus. The surgery was completed with no complications.

Approximately 6-7 months following the surgery, the patient began noticing gradually increasing dampness in her underpants requiring constant usage of Maxi pads. Eventually the Maxi pads required changing every 30 minutes leading to a transition to Poise pads (designed for bladder leakage), which she needed to change every 1-2 hours. The fluid would also soak through tampons. The liquid was clear, non-viscous, and odorless, similar in consistency to water. The non-stop, watery discharge greatly affected the patient's quality of life, as she would often leak through her pad, garments, and onto furniture. She viewed her condition as “intolerable,” and felt as if she “couldn't leave the house.”

The patient initially saw a urology consultant in August of 2010 for her symptoms. Physical exam was normal. A thorough evaluation for vesicovaginal and ureterovaginal fistulas was performed including computerized tomography scan with and without contrast, voiding cystourethrogram, intravenous pyelogram, and vaginal contrast exam. All studies were negative. Pelvic, transvaginal, and abdominal ultrasounds were noncontributory. Urodynamics reports showed normal bladder capacity and were negative for detrusor instability and stress urinary incontinence.

Malignancy was suspected owing to her idiopathic, profuse watery discharge. The patient underwent a total laparoscopic hysterectomy in October 2010, involving removal of the uterus and cervix, with bilateral salpingo-oophorectomy. Pelvic washing was negative for malignant cells, and pathology showed no malignant changes. Following surgery, the patient was still experiencing profuse, watery discharge. The patient was then referred to urogynecology in August of 2011. She was diagnosed with genuine stress incontinence and underwent insertion of a tension-free sling. The fluid production decreased by approximately 50% after this procedure, but the patient continued to experience great morbidity.

When the patient first presented to our dermatology clinic, we evaluated her already extensive workup. We believed her increased fluid production to be secondary to her prior gynecologic surgery and similar in pathophysiology to iatrogenic hyperhidrosis. A starch iodide test was not performed because the results would have been equivocal, as the affected area is typically moist at baseline.

The patient's treatment began by placing her in the Trendelenburg position. Two 3 cc syringes were each filled with 2.5 cc (100 units) diluted in a 4 unit per 0.1 cc concentration. The first syringe was used to introduce onabotulinum toxin A (commercial brand Botox) using insertion of a needle-less syringe via the introitus in an effort to coat the vaginal walls. The syringe was pushed deep in the vaginal vault and then the onabotulinum toxin gradually discharged while moving from the deep to superficial aspect of the vault. The second stage of the procedure involved a 4x4 gauze pad that was wrapped around a needle driver and nearly fully inserted into the vaginal vault with only a very small portion visible exteriorly. After insertion, the gauze was slowly saturated using the second syringe of onabotulinum toxin, hoping the gauze pad would serve as a wick in order to gradually deliver the agent to the vaginal walls as well as preventing the onabotulinum toxin injected initially from leaking out. This gauze was left for approximately 10 minutes with the patient remaining in Trendelenburg during that time, and was removed by the patient 3-4 hours after the clinic appointment.

The patient has experienced almost complete relief from her symptoms, and only notices mild return of symptoms a few days to weeks before her next appointment time. She receives her Botox treatment every 3-4 months and her quality of life has greatly improved overall.

## Discussion

Our literature review of female genital cosmetic and reconstructive surgeries did not yield any postoperative complications similar to our patient's: chronic, excessive vaginal or perineal discharge in the form of a clear, odorless fluid with an onset 6-7 months after surgery. Although we are still uncertain of the etiology behind our patient's symptoms, the parallels between her presentation and that of Frey syndrome are evident. Frey syndrome is a condition of gustatory sweating and flushing related to aberrant nerve regeneration following parotidectomy. The regenerating parasympathetic postganglionic nerve fibers (intended for the parotid gland) instead feed the sympathetic nerve fibers that innervate the local sweat glands [7].

Frey syndrome is experienced by approximately 3% of patients after a parotidectomy, with a mean duration after surgery of 9.6 months [8]. Our patient reported symptoms beginning 6-7 months following her perineoplasty and labial reduction, with a gradual increase in severity over time. This timetable and progressive augmentation of symptoms could be explained by the slow regrowth of peripheral nerves through Wallerian degeneration and subsequent regeneration, usually no more than 1 mm/day [9]. A final parallel between the two is our patient's response to treatment with onabotulinum toxin, resulting in complete resolution of her symptoms for periods of 3-4 months and highlighting a common cholinergic pathway.

We hypothesize that during our patient's surgery, pudendal nerve fibers supplying the perineum and vaginal mucosa were damaged and then aberrantly regenerated, promoting excessive, watery vaginal secretions. Terminal branches of the pudendal nerve provide autonomic and somatic innervation to the lower third of the vagina and extend to the perineum via Alcock's canal [6] (Figure 1). Her perineoplasty involved an incision in the vaginoperineal mucosa above the affected sclerotic tissue down to the perineal skin. The vaginal mucosa and perineal tissue were trimmed off above the stricture and undermining of the tissue up to, above, and beneath the hymenal ring was performed. Further undermining was done to bring the vaginal mucosa down to the perineal skin, indicating that terminal branches of the pudendal nerve were likely severed in the lower parts of her vagina where the undermining occurred.

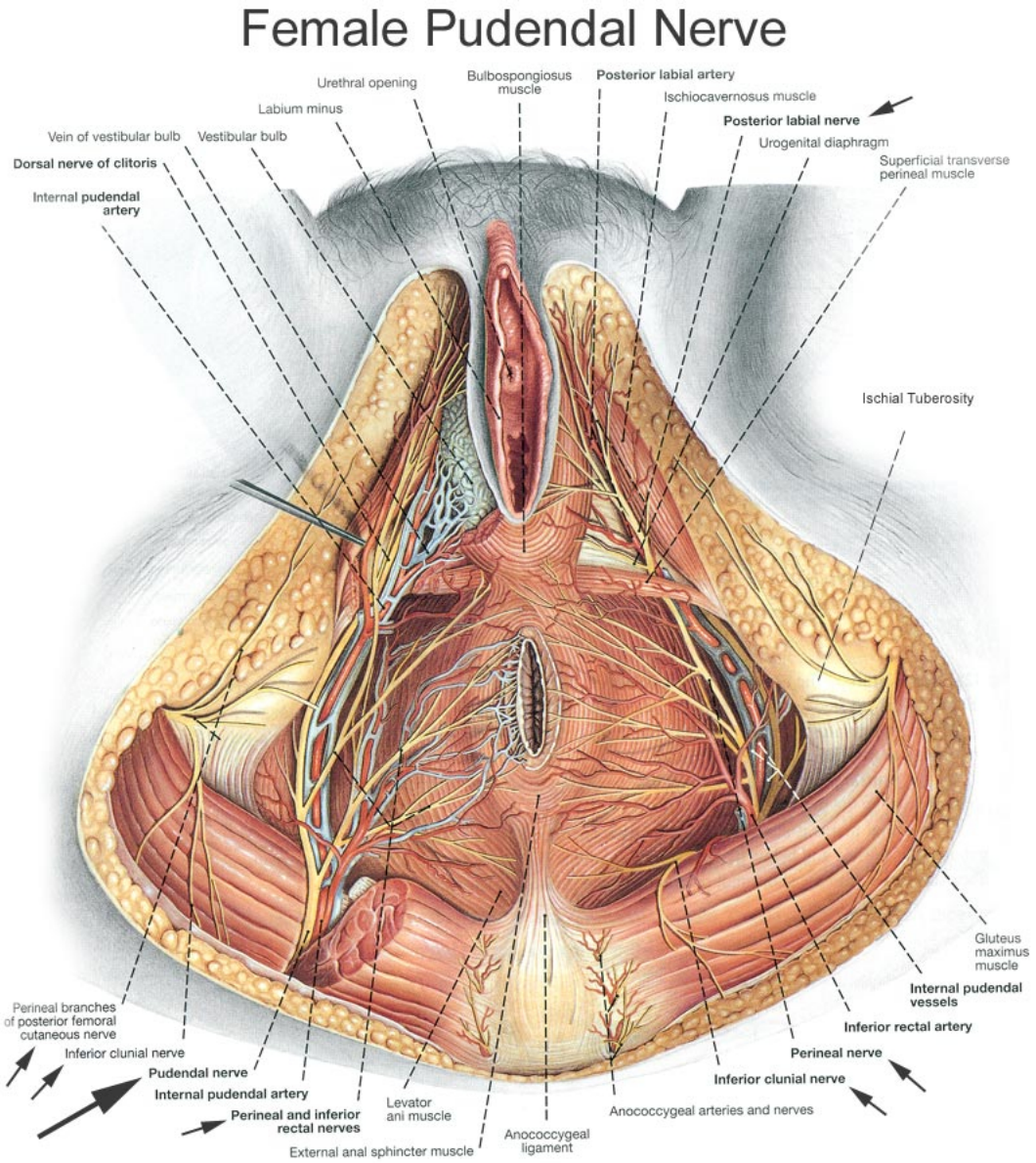

**Figure 1.** Female pudendal nerve anatomy. Diagram shows the pudendal nerve branching into the perineal and posterior labial nerves supplying the vagina and vaginoperineal regions. (Paulsen, Waschke, Sobotta Atlas of Human Anatomy, 15th Edition 2013 ©Elsevier GmbH, Urban & Fischer, Munich, permission granted.)

Although the vagina is devoid of glands histologically [10], secretory activity of cervical glands, promoted by parasympathetic innervation, contribute to vaginal lubrication; in addition, there is a rich network of blood vessels in the cervix, vagina, and labia (Figure 2). The blood vessels in the cervix, vagina, and labia are abundantly innervated by nerve fibers containing acetylcholine [6]. Had our patient's excessive secretions been uterine or cervical in origin, she would have experienced improvement or even vaginal dryness after her total hysterectomy, a side effect of hysterectomy cited in several studies [11, 12]. However, in our patient's case, the total hysterectomy did not ameliorate her watery secretions. The only intervention that did significantly decrease her secretions was onabotulinum toxin, which reduces the presynaptic release of acetylcholine. Although it may not be eccrine glands specifically affected in the vagina, it is important to recognize the usefulness of onabotulinum toxin in curbing excessive secretions in mucocutaneous surfaces and that aberrant nerve regeneration can affect the secretions of various tissues. Histopathological analysis may or may not confirm our hypothesis, but biopsy is an unnecessarily invasive intervention with no effect on management in this case. Furthermore, Frey syndrome, with similar onset and symptomatology, is a clinical diagnosis that does not require biopsy [13].

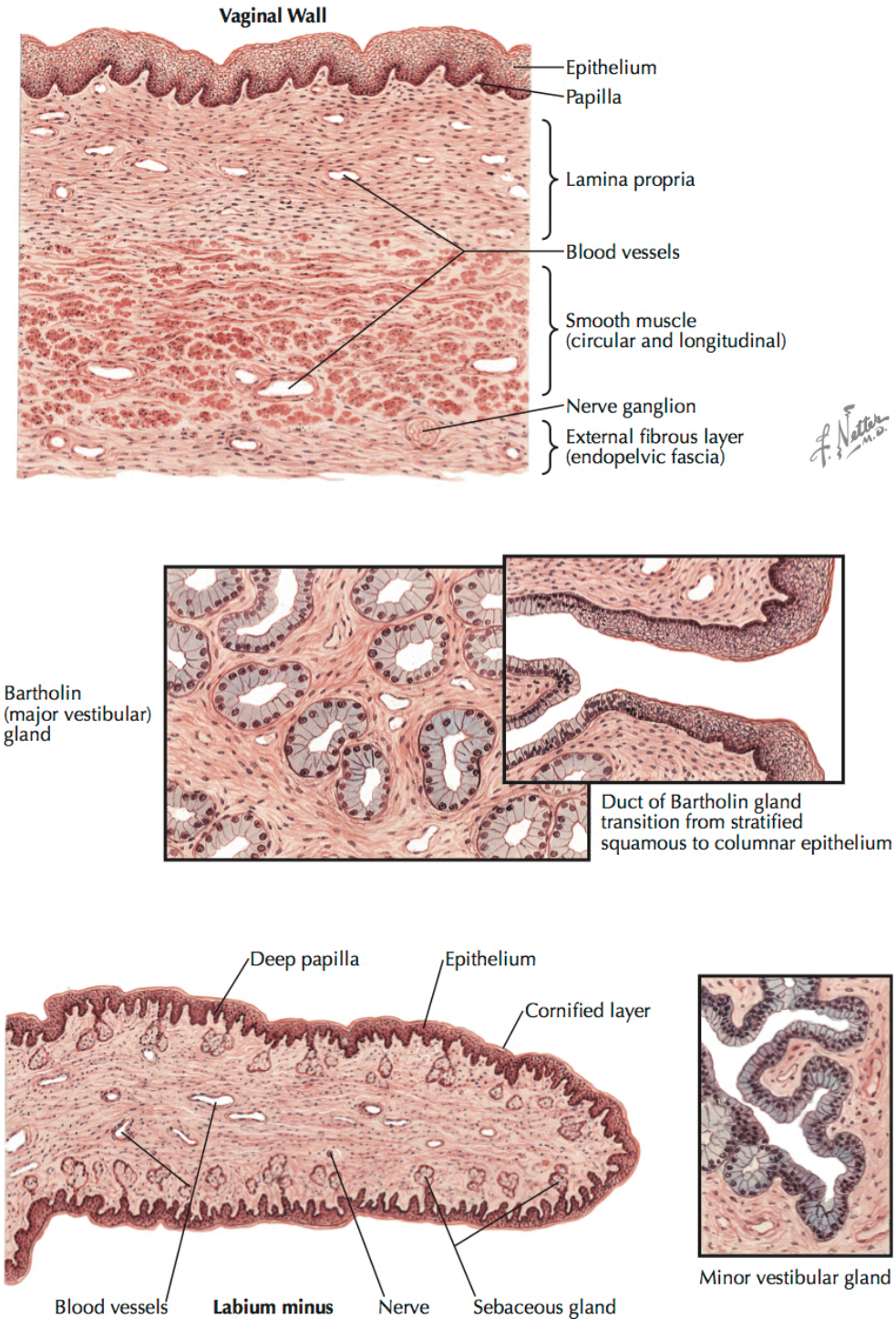

**Figure 2.** Histologic cross-section of the vaginal wall. The vagina is devoid of glands histologically, but a rich network of blood vessels contributes to vaginal lubrication under the control of smooth muscle and local nerve fibers, a major neurotransmitter of which is acetylcholine.


Onabotulinum toxin type A is FDA-approved for the dermatologic treatment of primary axillary hyperhidrosis (50 units per axilla), glabellar frown lines (20 units), and lateral canthral lines (24 units). Non-dermatologic indications include overactive bladder, cervical dystonia, upper limb spasticity, and chronic migraine, among others. For overactive bladder, the recommended total dose is 100 units injected across the detrusor muscle, whereas 200 total units is recommended for detrusor overactivity associated with a neurologic condition and 155 units for chronic migraine. In clinical trials of Botox for upper limb spasticity, doses ranged from 75 to 400 units, divided among selected muscles [14].

A total of 200 units per session was chosen for our patient, instead of a lower dosage, owing to the reliance on mucosal absorption rather than direct intradermal or intramuscular injection. This is well below the recommended maximum cumulative dose of 400 units in a 3-month interval for patients with multiple onabotulinum indications. Effects consistent with distant spread of the toxin and other adverse effects occur most frequently following off-label use in children with spasticity and at doses used in cervical dystonia and limb spasticity [14]. Furthermore, although lethal dose (LD50) calculations for humans are based on data from primates, it is projected that 2700-3000 units of onabotulinum toxin would be the LD50 for a 70 kilogram human being [15]. Onabotulinum injections for hyperhidrosis are typically well tolerated by patients, with results lasting from 4 to 16 months [3]. Our patient’s intravaginal treatments relieve her symptoms for at least 3 to 4 months without any adverse effects, which supports our hypothesis of genital hypersecretion secondary to aberrant innervation as the primary etiology of her symptoms.

One of the most interesting aspects of this report is the mode of delivery of the onabotulinum toxin. Whereas the product is typically injected via hypodermic needles, no perforation of the skin was necessary owing to significant mucosal absorption. With the vaginal vault difficult to access, the ability to deliver the medicine transcutaneously in a non-invasive manner was welcome to both patient and physician. We theorize that having the patient in a Trendelenburg position and insertion of an onabotulinum-soaked gauze pad prevented leakage of the medicine, thereby maximizing the effect.

## Conclusion

Given our patient's extensive workup that eliminated other etiologies for her genital discharge, we believe she developed a Frey syndrome-like, hypersecretory pathology in the genital region following her gynecological surgeries. The similarities between her presentation and that of Frey syndrome are extensive, including history of surgery in the affected area, time of onset of symptoms following surgery, nature of the symptoms, and response to treatment with onabotulinum toxin targeting a cholinergic pathway. Our patient's treatments have been simply administered in an outpatient dermatology clinic with no side effects. She has reported greatly enhanced quality of life. It is our hope that this report may stimulate further research in treating patients with rare and debilitating manifestations of iatrogenically-induced symptoms similar to secondary hyperhidrosis in mucocutaneous regions.

## References

1. Lear W, Kessler E, Solish N, et al. An epidemiological study of hyperhidrosis. Dermatol Surg. 2007;33:S69-S75. [PMID: 17241417]
2. Hornberger J, Grimes K, Naumann M, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol. 2004;51:274-286. [PMID: 15280848]
3. Lowe N, Campanati A, Bodokh I, et al. The place of botulinum toxin type A in the treatment of focal hyperhidrosis. Br J Dermatol. 2004;151(6):1115-1122. [PMID: 15606505]
4. Bolognia J, Jorizzo JL, Schaffer JV. Dermatology. Third Ed. Philadelphia: Elsevier Saunders; 2012.
5. Rohen JW, Yokochi C, Lütjen-Drecoll E, Won K. Color Atlas of Anatomy. Seventh Ed. Stuttgart: Schattauer; 2011.
6. Goldstein I, Meston CM, Davis S, Traish A. Women’s Sexual Function and Dysfunction: Study, Diagnosis and Treatment. Taylor and Francis: Boca Raton, FL; 2005.
7. Sethuraman G, Mancini AJ. Familial auriculotemporal nerve (Frey) syndrome. Pediatr Dermatol. 2009;26(3):302-305. [PMID: 19706092]
8. Moeller K, Esser D, Boeger D, et al. Parotidectomy and submandibulectomy for benign diseases in Thuringia, Germany: a population-based study on epidemiology and outcome. Eur Arch Oto Rhino Laryngol. 2012;270(3):1149-1155. [PMID: 23073736]
9. Wood MD, Kemp SW, Weber C, et al. Outcome measures of peripheral nerve regeneration. Ann Anat. 2011;193:321-333. [PMID: 21640570]
10. Mescher AL. Junqueira’s Basic Histology Text and Atlas. Twelfth Ed. McGraw-Hill Medical: USA. 2010; 408.
11. Schofield MJ, Bennett A, Redman S, Walters WAW, Sanson-Fisher RW. Self-reported long-term outcomes of hysterectomy. Br J Obstet Gynaecol. 1991;98:1129-1136. [PMID: 1760425]

12. Oldenhave A, Jaszmann LJB, Everaerd W, Haspels AA. Hysterectomized women with ovarian conservation report more severe climacteric complaints than do normal climacteric women of similar age. Am J Obstet Gynecol. 1993;168:765-771. [PMID: 8456877]
13. Rustemeyer J, Eufinger H, Bremerich A. The incidence of Frey's syndrome. J Craniomaxillofac Surg. 2008;36:34-7. [PMID: 18023355]
14. Allergan. Prescribing information: BOTOX® (onabotulinumtoxinA). 2015.
15. Panicker JN, Muthane UB. Botulinum toxins: pharmacology and its current therapeutic evidence for use. Neurol India. 2003;51:455-460. [PMID: 14742921]