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CHAPTER 14

Botulinum Toxin for Vaginismus

Ayman El Attar

INTRODUCTION

Women who suffer from this physical and psychological disorder may experience pain during sexual intercourse, gynecological examinations, or while inserting tampons. They tend to experience fear and anxiety that causes them to panic and withdraw from these situations. Vaginal penetration disorder is a major sexual problem with a negative impact on the patient, her partner, and even their family. Treatment of vaginismus is still a big challenge and often without success.

The successful treatment of vaginismus in our center started in 2018 using our protocol of injecting botulinum toxin in the bulbospongiosus muscle 50–200 units according to the severity of the case.

In 1862, the father of modern gynecology James Marion Sims **(Fig. 1)** coined the term vaginismus to describe recurrent and persistent involuntary contractions of perineal muscles during penetration, resulting in anxiety, fear, and pain.[1] The prevalence of vaginismus varies significantly between developed and developing countries. This could be attributed to cultural differences and ranges. The great variation of reporting the prevalence ranged from 1 to 60%.[2-4] The American Psychiatric Society has defined vaginismus as "an uncontrollable contraction of the muscle of one-third of the external vagina that prevents intercourse."[5] According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), vaginismus is under the category of genitopelvic pain/penetration disorder.[5,6] The World Health Organization has emphasized the pain associated with vaginismus and categorized it as a disorder of female sexual penetration pain in its International Statistical Classification of Diseases and Related Health Problems, 11th edition (ICD-11).[7]

Fig. 1: James Marion Sims (January 25, 1813 to November 13, 1883).

The term "vaginism" describes an involuntary, recurrent, or persistent contraction of the perineal muscles surrounding the lower third of the vagina or the orgasmic plateau. It occurs during sexual intercourse and/or penetration or during a gynecological examination with a speculum.

A controversial American physician is considered the "Father of modern gynecology," who developed a surgical technique for the repair of vesicovaginal fistula and used enslaved African-American women, without consent or anesthesia, as experimental subjects. He was regarded by many modern historians as highly unethical. He described it as "a prime example of progress in the medical profession made at the expense of a vulnerable population."

In 1862, he described vaginismus as a reflex-like contraction of circumvaginal musculature, resulting in nonconsummation of marriage. This condition is characterized by spastic, painful, and uncontrollable contractions of the vaginal muscles, which makes any attempt at penetration feel as if there is a wall or barrier to the vaginal canal. Theories behind vaginismus.

PREVALENCE

Half the world's female population suffers from some kind of sexual dysfunction. Vaginismus affects up to 7% of women, a figure that may represent an underestimation.

PATHOGENESIS OF VAGINISMUS

The exact etiology of vaginismus remains elusive. Multiple theories and various predisposing factors for vaginismus have been proposed. Strict religious prejudice and upbringing in a sexually sinful context with a negative psychological outlook on sex. This will predispose the female to apprehension toward first-time sex, sexual myths, and anxiety during gynecological examinations. Other theories postulated are the impact of the history of sexual and physical abuse, upbringing in a conflicting family, cultural taboos, and lack of sex education.

Many other factors have been found to predispose to vaginismus including sexually transmitted diseases, vaginal atrophy, pelvic inflammatory disease (PID), and endometriosis. Congenital abnormalities, such as hymen anomaly, scarring from trauma, and cancer, may also induce vaginismus.

ETIOLOGY

- Strict religious beliefs
- *Strict sexual beliefs:* Pain, bleeding, and injury
- History of sexual abuse at a young age (two times more common in vaginismus patients)
- *Organic causes:*
  - Sexually transmitted disease (STD)
  - Endometriosis
  - Hymenal abnormalities
  - Trauma associated with genital surgery
  - Radiotherapy
  - Vaginal atrophy
  - Pudendal neuralgia
  - Pelvic inflammatory disease
  - Pelvic organ prolapse
  - Vaginal lesions
  - Vaginal tumors
  - Diabetes mellitus
  - Multiple sclerosis
  - Spinal cord injury

DIAGNOSIS

Take a detailed history of each patient keeping in mind the previous causes. Stage the degree of vaginismus, i.e., mild to severe. Differentiate between psychological causes and true vaginismus.

CLASSIFICATIONS OF VAGINISMUS

According to the ICD-11 and the DSM-5, vaginismus can be classified as either primary, when a woman has never had intercourse or acquired, or secondary, when a woman loses the ability to have penetration, usually as a result of acquired dyspareunia secondary to physical events, mental and psychological factors, and infection or menopausal changes. Furthermore, vaginismus is classified as total vaginismus, where intercourse is not possible, and partial vaginismus, in which intercourse is possible but causes genital pain.[5,7-9]

Vaginismus was first described in 1978 by Lamont, who divided the pathology into four degrees according to the severity of the condition:

1st degree	• Levator and perineal spasm relieved with reassurance • Able to tolerate vaginal examination
2nd degree	• The perineal spasm is maintained through the gynecology examination • Unable to relax for the pelvic examination
3rd degree	• Spasm of the levator muscle • Guarding by elevation of buttocks during a pelvic examination
4th degree	• Perineal and levator spasm • Adduction of thighs, elevation of buttocks, and unable to tolerate the pelvic examination

DEVELOPMENT OF VAGINISMUS TREATMENT

As procreation defines marriage and a healthy sexual life, vaginismus affects a couple's emotional health within their marriage; thus, the treatment and improvement of vaginismus are of chief importance.[3,10]

Repeated episodes of vaginismus and failed intercourse may affect the sexual health of a woman, decreasing her self-esteem and adversely impacting her marital relationships leading to marital discourse, infidelity, and ultimately separation or divorce. Currently, due to the variable efficacies of different current therapeutic interventions, no standard approach has been proposed to date.[4,6,9]

Vaginismus also contributes to vaginal atrophy and dyspareunia. Treating these problems can help to ameliorate coital pain.

Considering the physical and behavioral factors, various treatment modalities include cognitive and behavioral therapies, relaxation methods, sex education, local anesthetic agents, psychotherapy or sex therapy, and physiotherapy of pelvic muscles.

While mild vaginismus may respond to modalities and conventional therapies, severe forms require interventional therapies, such as botulinum toxin injections.

Botulinum neurotoxin type-A (BoNT-A) is a polypeptide produced by gram-positive anaerobic bacillus *Clostridium botulinum*. It is made of a zinc-dependent endopeptidase 50 kDa short chain and 100 kDa long chain which attach to the high-affinity motor never vending cell membrane receptors. The short chain will cleave the membrane-associated 25-SNAP protein rendering the release of acetylcholine from vesicles in the nerve-ending cytoplasm impossible. Following its use in vaginismus in 1997, many researchers have explored the use of botulinum toxin in the treatment of vaginismus and have conferred that treatment with botulinum toxin is a safe and effective modality that inhibits vaginal muscle spasm and helps to achieve painless intercourse.[11]

However, limited studies are available comparing the efficacy of different Botox doses in the treatment of vaginismus; thus, we proposed a dosing regimen based on the severity of symptoms as explained in the treatment section.

Muscles of the lower one third of the vagina, circumvaginal muscles according to a publication by Van de Wiel in 1990. Lamont in 1994 published that the main muscles involved are bulbocavernosus, levator ani, and pubococcygeus.

WHY IS BOTULINUM TOXIN USED FOR VAGINISMUS?

It was first described by Brin and Vapnik in 1997. Botulinum toxin is a muscle relaxant that can weaken or stop any muscle's ability to contract, including the vaginal muscles. Botulinum toxin doses are administered according to the size of the target muscle, so larger muscles require larger doses.

In the treatment of vaginismus, the procedure is done with an in-office nitrogen delivery system to suppress the fear and anxiety that vaginismus sufferers often experience during gynecological examinations or any form of general touch to the pelvic area.

This treatment protocol not only helps the patient remain relaxed and comfortable as the Botulinum toxin is injected, but also facilitates progressive dilation of the vagina for the insertion of the larger dilators.

Muscles contributing more to the vaginismus symptoms are determined at the time of examination. Botulinum toxin can be injected into one, a combination, or all of the three vaginal muscles responsible for the patient's uncontrollable vaginal spasms, with the dose being divided to inject a larger volume of Botulinum toxin into the more powerful muscles. The pubococcygeus muscle group as part of the pelvic floor muscles, often resembles a tightly drawn fist in the most severe vaginismus cases, and it is usually the muscle that receives the largest dose of the toxin.

BOTULINUM TOXIN RECONSTITUTION AND HANDLING

Before the treatment, one vial of frozen Botox containing 100 U was diluted with 2 mL of preservative-free saline without shaking to prevent foam formation. The procedure was conducted either under local or general anesthesia based on the patient's comfort. In the Botox 150 U group, Botox 50 U (1 mL) each was injected into the bulbospongiosus muscle and the lateral submucosal areas of the introitus, marked by the residual hymenal fragments, at 9 o'clock and 3 o'clock positions using a 1 mL insulin syringe. In the Botox 200 U group, 75 U (1 mL) was used and injected into the areas similar to the Botox 150 U group. In patients with persistent spasms and tightness of the levator ani muscle, an additional 50 U was injected subcutaneously into the perineal body in both groups. To avoid urinary and rectal incontinence, care was taken not to inject the solution anteriorly or posteriorly. In some patients, an additional hymenectomy was done. Following injections, a medium-sized plastic speculum was inserted into the vagina for 6 hours. The patients were initially followed up after 2 weeks, and the postoperative outcome was recorded using a similar preoperative questionnaire. All patients were followed up for a year over phone calls.

Keep the vial refrigerated (2–8°C). Xeomin does not require refrigeration. In nonreconstituted form may store for up to 24 months (do not use beyond expiration date). Reconstitute with 2.5 cc of 0.9% nonpreserved sodium chloride (NaCl) for 4 hours up to 6 weeks if refrigerated.

Store after reconstitution in the refrigerator between 2°C and 8°C. The toxin may be stored for 4–6 weeks (with 87% potency). Using the reconstitution needle 21G 1.5 inch, draw up the proper amount of saline.

The toxin should be clear, colorless, and free of particulate matter. Insert the needle straight into the vial, then tilt the vial at a 45° angle. Slowly inject the saline into the vial. Vacuum demonstrates that the sterility of the vial

is intact. Do not use the vial if the vacuum does not pull the saline into the vial. Release the vacuum by disconnecting the syringe from the needle and allowing air to flow into the vial. Gently mix with the saline by moving the vial side to side or rotating the vial. Draw the fluid into the injection syringe by placing the needle into the bottom corner of the vial for full extraction.

Use a reconstitution sticker to record the date and time of reconstitution, the amount of diluent added, the resulting dose to be administered, and the filled syringes stored in a refrigerator.

INJECTION TECHNIQUE

Botulinum toxin is injected above the hymenal ring in the insensitive middle third of the vagina into the vaginal side walls in vaginismus patients; the urethra and rectum are carefully avoided to prevent urinary incontinence. The exact points should be as demonstrated in the **Figure 2** located at 2-3-4 o'clock and 8-9-10 o'clock while the patient is in the lithotomy position. The injection should be performed using 1 mL syringes attached to a 13-mm 34G needle. The entire needle should be inserted into the depth of the lateral vaginal wall with the needle hub touching the vaginal mucosa.

It is possible to treat grades 1–3 while patients are awake or using nitrous gas or oral sedation. In the case of grade 4, patients have to be treated under general anesthesia.

Once injected into the vaginal walls, Botulinum toxin begins to take effect in 2–5 days and reaches a maximal effect within 7 days. Weakening even a portion of the affected vaginal muscles blocks their ability to fully contract and eventually go into spasm, making the muscle more flexible and easier to stretch with dilators or during intercourse.

HOW OFTEN IS BOTULINUM TOXIN USED TO TREAT VAGINISMUS?

In most cases, a single treatment is sufficient. Once the vagina is progressively stretched, and the patient can experience pain-free penetration, a second round of injections is rarely necessary. Once the vagina remains relaxed and dilated for 12 months, the affected vaginal muscles are less likely to resume their spastic nature. Once the patient achieves pain-free penetration and intercourse with dilators, the neural response that previously triggered vaginal spasms, fear, and anxiety upon penetration gradually shuts down.

Dose Recommendation

According to vaginismus, grade does vary. Most therapeutic failures happen because of the undertreatment of the patients. Botulinum toxin's lethal dose is 30 IU/kg, so it is a safe product to use even in large doses. The points of needle entry are demonstrated in **Figure 2**.

Vaginismus Grade	*I*	*II*	*III*	*IV*	*V*
Dose (U)	25 × 2 = **50**	50 × 2 = **100**	75 × 2 = **150**	100 × 2 = **200**	
Points	2 × 2	3 × 2			

Adjuvant Therapies

Platelet-rich plasma with its multitude of growth factors has been demonstrated to be of additive therapeutic value. It is the author's practice to administrate it in the same session. Tadalafil (Cialis) 2.5 mg per os (PO) daily for 30 days is also given to the patient.

Although there is no scientific evidence of any actual muscular fibrosis in vaginismus patients, the use of dilators by self-insertion 10 days after the treatment will help to alleviate the fear of pain in most patients. If patients can comfortably self-insert the dilator's place, intercourse should become simpler and painless. While the fear of penile penetration may initially remain in some patients, the anxiety surrounding penile penetration tends to subside rather quickly as they transition into intercourse. Daily use of vaginal dilators from day 10 post-treatment for 15 minutes every night.

No significant difference was found in comparing low-dose Botox (150 U) versus high-dose Botox injections (200 U) in vaginismus patients. However, it is estimated that it affected 57% of women in childbearing years in some studies.[12] Overall, the patients' mean [standard deviation (SD)] age in our study was 30.2 (8.3) and similar between both groups. The mean age of vaginismus patients was in accordance with a study by Yule[13] (28.8–30.8 years) and

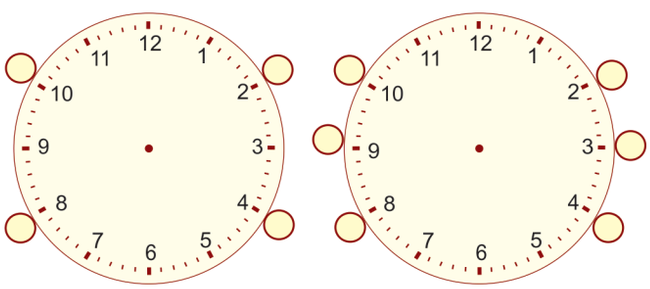

Fig. 2: Legend to be provided by the author.

slightly higher than the mean age of patients (21–28 years) reported in the literature.[3,9,10] The difference could be due to late marriages and cultural taboos; women do not openly speak up about sexual problems. According to previous studies, the self-reported duration of vaginismus ranges from 3 months to 44 years.[3,14–16]

In our study, the mean duration of vaginismus was 19.3 months (range: <1–96 months). The shorter duration of our study could result from religious and cultural norms where procreation is considered an important aspect; many women approached marriage at an earlier stage.[15] Patients who never experienced nonpainful intercourse comprise the primary vaginismus group; those who acquired vaginismus later in life are categorized as secondary vaginismus. In our study, the frequency of primary vaginismus (88.9%) was higher than secondary vaginismus (11.1%). The findings are in accordance with previous studies.[14,16] Similar to the study by Velayati et al.,[17] (88.6%) approximately 90% of patients were nulliparous in our study.

Based on the Female Sexual Function Index (FSFI) questionnaire, more than half of patients had anxiety and pain scores of 10, suggesting severe anxiety and impossible or extremely painful, respectively. Sexual and reproductive health are considered the defining factors in the well-being of a person.[18] Inability to have intercourse negatively affects an individual's marital satisfaction, stability, overall health, and quality of life.[19,20] Therefore, treatment of vaginismus at earlier stages of marriage is the need of the hour. Various treatment modalities for vaginismus management include physical therapy, Kegel exercises, counseling, psychotherapy, muscle relaxants and lubricants, vaginal dilators, cognitive-behavioral therapy, topical anesthetics, antianxiety medications, use of benzodiazepines, hypnotherapy, and Botox injections.[4,9,12] However, none of the treatment approaches are evaluated based on well-designed studies.

Botox injection effectively treats neuromuscular dysfunctions and has been widely used since the successful treatment of the first case in 1997.[21] Botulinum toxin is a protein neurotoxin produced by anaerobic sporulated bacteria of the *Clostridium* genus.[22] It induces peripheral muscle relaxation by degrading soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) proteins and blocking the release of acetylcholine responsible for neurotransmission of muscle contraction. Additionally, Botulinum A also decreases the substance P and glutamate levels as a part of central sensitization, thereby decreasing pain sensitivity.[23] The muscle inactivation lasts until the formation of new fibrils and reconnection of the neuromuscular junction.[24] The following factors must be considered during the delivery of Botox injections: The amount of Botox injected per muscle and the total amount and the number of sites injected.[24] To avoid antibody formation, the dose and frequency of Botox should be minimized. Although the extent of paralysis depends on the amount of toxin injected, the data on the minimum dosage required for vaginismus treatment are unclear. Botox doses ranging from 20 to 500 units per injection are deemed successful in treating vaginismus and pelvic pains.[12,23,25] In a comparative analysis, Ghazizadeh et al.[26] reported that a higher dose of Botox (500 U) is more effective than a lower dose (250 U) of Botox. Our study aimed to compare the efficacy of low-dose Botox (150 U) with higher-dose Botox (200 U) in vaginismus patients' treatment outcomes.

Pacik et al.[16] explained a direct relationship between muscular spasms and the severity of vaginismus. Spasms of increased muscle activity in levator ani, puborectalis, and bulbocavernosus muscles are common in severe vaginismus grades. Therefore, similar to Park and Paraiso,[27] in our study, Botox was injected explicitly into and around the bulbospongiosus muscle and the lateral submucosal areas of the introitus and additional injections into the levator ani muscle, wherever required. Successful paralysis or spasm of the bulbospongiosus muscle is indicative of improvement in vaginismus.[28] According to the manufacturer's instructions, we diluted 100 U of Botox with 2 mL of preservative-free saline. Reports also suggest replacing saline with anesthetic solutions for immediate antinociceptive effects. However, it must be used with caution.[25]

The ability to achieve satisfactory intercourse is considered the primary outcome in most studies.[8,9,24,29,30] Based on this, the success rate of botulinum injections in vaginismus ranges from 62% to 100%,[23] and patients achieved satisfactory intercourse on the same day of treatment.[9] In our study, Lamont criteria and psychosexual evaluation using a questionnaire by FSFI were used as indicators to check the efficacy of botulinum toxin in a broader perspective. Similar to Bertolasi et al.,[31] we observed significant improvement in finger penetration pain and anxiety scores, dilator anxiety and pain scores, and intercourse anxiety scores in individual treatment groups (p <0.05). In intergroup comparisons of symptom improvements between 150 U and 200 U Botox, except for

dilator pain scores ($p = 0.015$), the pain and anxiety scores of all other variables in both treatment groups were similar ($p > 0.05$).

Based on an Iranian study, factors including male partner involvement during treatment and cultural background not influencing the treatment outcome,[32] whereas marital and fertility-related anxiety, family and social pressure, and personal guilt negatively affect the treatment outcome.[33] According to Anğin et al.,[34] a positive history of vaginismus within a close family and environment negatively affects the treatment outcome. Additionally, sexual abuse decreases the prognosis. While the sexual health of the male partner does not influence the treatment outcome, it affects the duration of treatment. In our study, occupation, residency, type of vaginismus, and type of anesthesia did not significantly affect the overall study cohort's treatment outcome and individual groups.

Although botulinum toxin is generally safe, its use is contraindicated in patients with local infections, albumin hypersensitivity, neuromuscular and bleeding disorders, and the use of anticoagulants.[23] Adverse events are noted with higher doses that include pain, hematoma, and infection at the injection site, urinary and anal incontinence, transient blurred vision, and vaginal dryness.[14,25,35] However, urinary and fecal incontinence are seen in higher doses >100 U. Rarely, an ischiorectal fossa abscess may also occur.[36] To prevent injection-related adverse effects and complications, guidance techniques, such as electromyography, electrical stimulation, and ultrasound, can be used in an office setting to restrict injections to the muscles and vaginal soft tissue only. In our study, since the clinician was careful not to inject the solution anteriorly or posteriorly, side effects were seen in only 19.2% of patients (urinary incontinence versus anal incontinence; 17.2% vs. 2%). The frequency of side effects between the 150 U and 200 U Botox groups was comparable ($p = 0.997$).

In a country with strict social and religious norms where sexual problems are considered taboo, the present study is the first of its kind with the hope of saving families from breaking apart due to vaginismus-related consequences. The inclusion of a wide range of patients from within and outside the country was one of the strengths. Although the sample size was small, it seemed sufficient to identify differences in the study outcome. A short follow-up period is one of the study's major limitations, as previous studies have reported recurrences following Botox injections. According to previous research, a placebo had an equal or superior effect to Botox injections.[37,38] In their metanalysis, Weinberger et al.[39] conferred that the placebo effect accounts for 67.7% of outcomes in female sexual dysfunction treatment. The inclusion of a placebo arm will assist in assessing the accurate outcome of the test group. Hence, the inability to include a placebo arm in the study was another limitation. Therefore, further placebo-controlled, prospective randomized trials with controlled questionnaires are essential for vaginismus treatment.

In vaginismus patients, detailed discussions and history are mandatory to categorize a patient under an anatomical or psychological disorder, especially during the first gynecological visits. The botulinum injection is a simple, safe, cost-effective, and rapid treatment that can be performed in an inpatient or outpatient setting; clinicians widely appreciate it. However, the effect lasts for around 6 months. Based on the evidence, the frequency of patients discontinuing follow-up ranges from 1.2% to 47.8%.[34] Therefore, regular follow-ups may be required to check for recurrences. Severe vaginismus is one of the reasons for unconsummated marriages, and continuous failure to have intercourse secondarily leads to male impotence.[40] The fear and anxiety about sex could be due to a lack of sex education in women with no knowledge of sexual anatomy.[41] Therefore, it is of utmost importance to incorporate sex education into the school curriculum.

Moreover, some studies demonstrated no positive or inferior outcome of Botox in vaginismus as compared with other treatment modalities, including physiotherapy,[4] behavioral sex therapy,[42] and better outcomes with a multimodal approach, such as dilatators, physical therapy, psychotherapy, and sacral erector spinae block (ESB).[6] Therefore, pre- and postprocedure counseling and long-term follow-up are essential during vaginismus treatment. Along with satisfactory intercourse, domains of sexual function and FSFI must also be considered efficacy endpoints of vaginismus treatment.[4,42]

Along with Botox injections, it is paramount to incorporate psychotherapy and counseling in patients, especially those with severe anxiety, and fear of sex and gynecological examination. Further randomized controlled trials, including a placebo group, are warranted to evaluate the efficacy of low-dose Botox.

Several pathologies from the gynecological field for which BoNT treatment can be used. Most of these dysfunctions have been shown to be refractory to

conventional treatments, but the results after single or repeated cycles of BoNT-A were favorable and the symptoms improved.

The dosage used ranged from 40 U to 400 U in a single administration. In some cases, repeated injection cycles were necessary, depending on the symptomatology and the scores obtained after the patients completed standardized questionnaires. The improvement of the symptomatology was objectively certified using standardized questionnaires before and after a certain period postinjection.

CONCLUSION

When compared to BoNT-B, we observed that BoNT-A is used more often with good results, especially because the paralysis resulting from BoNT-B is not as efficient as the one of BoNT-A. It is also desirable to carry out further studies to reach a consensus on the optimal BoNT-A dose and administration protocol to create a standardized treatment.

This review highlights that BoNT could be successfully used in treating symptoms of gynecological dysfunctions refractory to conventional treatments, having few side effects and high efficacy.

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