The Genito-Pelvic Pain/Penetration Disorder Paradigm and Beyond

Spoelstra, Symen Kornelis

CHAPTER 9

Summarizing discussion and future perspectives

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) the female sexual pain disorders vaginismus and dyspareunia have been merged into the genito-pelvic pain/penetration disorder (GPPPD).(1) The principal reason behind this merging is that in clinical practice it always has been difficult to make a categorical distinction between dyspareunia and vaginismus. Generally, these two female sexual pain disorders are considered to lie on a phenotypical continuum. Nevertheless, a growing body of evidence has emerged over the past few years to suggest that lifelong vaginismus and dyspareunia are indeed two separate entities.(2-3) In this thesis we approach this paradox from different perspectives.

Provoked vestibuldodynia (PVD) is the most frequent cause of chronic superficial dyspareunia in premenopausal women.(4) Until now, there is no plausible Dutch translation for this condition. The pain in PVD is provoked specifically by touch, pressure and vaginal penetration.(5) Its aetiology is multifactorial and its pathophysiology is yet unknown. PVD often leads to sexual, psychological and/or relational problems.(6-7)

The subject of this thesis is the pathophysiology and clinical management of PVD. The way this subject is investigated can best be described as rooted in the Psychosomatic Obstetrics & Gynaecology tradition. In the literature on Psychiatry and Psychotherapy this approach is described as the '*scientist practitioner-model*'. Where scientist refers to the process of fundamental reflection by doing research, the term practitioner refers to '*on-the-job-experience*'. One of the main characteristics of this tradition is *'building the bridge from two sides'* to connect theory with clinical practice. The main purpose of using this approach in this thesis is twofold: 1) to evaluate the clinical treatment of PVD, and 2) to gain more insight into the pathophysiology of vaginismus and dyspareunia.

Although formulated as two separate questions, these questions are highly interrelated by a mechanism known as clinical reasoning. Clinical management of PVD is based on clinical reasoning, represented by the aetiology-diagnosis-treatment trias. The rationale for this entire research project, the *'raison d'etre'*, lies in the fact that in PVD the explanation model on which diagnosis and treatment are (supposedly) grounded, is incomplete. In PVD there is no clear (linear causal) relationship between pathology and complaints. In order to be able to understand the underlying mechanisms, as a clinician one has to rely on careful and detailed chronological history taking. Subsequently, it often becomes clear that PVD symptoms in the beginning show up as normal psychophysiological protective functions. After a while, however, they seem to transform into 'inappropriate' symptoms: complaints. The link between the owner, the patient, and their protective function somewhere gets lost underway. This means that, in contrast to 'normal'

pathology (sic), primarily, the 'cause' of PVD symptoms probably does not lie in the phenomenon itself, but in its contextual (in)appropriateness, i.e. the (mis)match between action and reaction.

A central question is why normal adaptation, with regard to perception and/or (sexual) behaviour, does not take place under seemingly normal circumstances. To understand why and how normal psychophysiological reactions have become too extreme, too prolonged, and/or too intense, PVD symptoms should always be put into a biopsychosocial perspective. From this perspective, different treatments can be initiated. In such a case, this is referred to as a multidimensional approach. This thesis starts with **chapter 1**, which describes the symptoms, aetiology, pathogenesis, differential diagnosis and treatment of PVD based on the case history of a young woman with PVD. Arguments are put forward why a biopsychosocial approach is required. Pain and fear of pain are key elements in PVD. Both of these elements are normal psychophysiological protective functions that are appropriate in situations of real or threatened danger. However, in PVD, they overshoot their purpose and become too extreme, too prolonged, and/or too intense. Apparently, there are often concealed and subconscious reasons for such a reaction. In this case, we are dealing with functional complaints, and consequently a bio-medical explanation model does not adequately fit the bill. The most important element in the treatment is ultimately to break the vicious circle of pain and fear. However, even after successful treatment - as this thesis will demonstrate - when resuming sexual intercourse, caution is warranted while having intercourse.

To provide some insight into the clinical management of PVD, we firstly discuss the results of our treatment studies.

PART I: TREATMENT

The pharmacotherapy of PVD consists mainly of local application of anaesthetic or fatty ointments. In addition, antidepressants(8) and anticonvulsants are sometimes prescribed. Anticonvulsants are known to relieve pain in neuropathic pain conditions. (9) As discussed in **chapter 2,** based on the assumption that in PVD the pain has a neuropathic character, anticonvulsants (gabapentin, lamotrigine and carbamazepine) have occasionally been prescribed for the treatment of vulvodynia.

Eight relevant studies on gabapentin and lamotrigine in vulvodynia were found; two case reports, three retrospective studies, two non-randomized studies and one open-label pilot trial. Seven out of these eight studies focused on the efficacy of gabapentin, while one study focused on lamotrigine. It is remarkable that we did not find any studies

on the use of carbamazepine in the treatment of vulvodynia.
Success rates with gabapentin to reduce vulvar pain ranged from 50 to 82%. In the lamotrigine study 'substantial' pain relief' was reported and satisfaction with symptom relief was 82%. These results seem promising, but the studies have several methodological weaknesses. Assessment of the quality of these studies with the Oxford Centre for Evidence Based Medicine levels of Evidence revealed insufficient convincing evidence to support the use of these anticonvulsants.
However, their prescription based on the clinical expertise of the gynaecologist should not be eliminated altogether. The results of some of the reviewed studies suggest that anticonvulsants were beneficial in symptom relief in at least some of the women with vulvodynia. Of course, patient care should be as evidence-based as possible, but not at the expense of a patient-based comprehensive approach. It is essential to combine clinical expertise with the needs of each individual patient. This is particularly important in case of treatment for therapy-resistant disorders such as PVD. However, to get a more definitive answer to the efficacy of anticonvulsants pharmacotherapy for the treatment of vulvodynia prospective studies are needed with a double-blind, randomized controlled design.

Although a one-dimensional approach, as anticonvulsant mono-pharmacotherapy is preferable to assess the therapeutic outcome of one specific intervention, it is also limited in its scope and impact. This is especially the case in PVD because its burden goes far beyond the experience of pain during intercourse. The majority of treatment studies on PVD used a one-dimensional approach and based their treatment success exclusively on the degree of persistent coital vulvar pain. This approach seems too limited. Including other criteria in the evaluation, such as sexual functioning and sexual related psychological stress, will increase the number of treatment goals. Subsequently, a multidimensional approach is required. PVD should be considered as a heterogeneous, multisystemic and multifactorial disorder and has to be treated accordingly.
As identified in **chapter 3** the efficacy of the multidimensional treatment approach to PVD in our medical centre was examined retrospectively in 64 women. The treatment resulted in long-term vulvar pain reduction in 81% of the women (mean follow-up 5 years). Eighty percent had resumed intercourse after treatment and 80% would recommend a similar treatment approach to other women with PVD. Although pain reduction was reported in 81%, only 8% of the patients reported complete painless sexual intercourse, i.e. 92% of the women still mentioned pain while having intercourse. Not surprisingly, compared to a matched Dutch norm group, sexual functioning scores in our study group were significantly lower and scores for sexually related personal distress significantly

higher. It was striking that there were no significant differences in relational sexual satisfaction. These women and their partners were able to adjust somehow to the circumstances, at least in terms of relational sexual satisfaction, despite the continuing (although less intense) vestibular pain. Apparently this made the treatment in the eyes of patients worthwhile, explaining the women's positive advice to fellow sufferers to undergo such a treatment as well. In literature, it appears that PVD is not necessarily associated with general relationship maladjustment of the woman and her partner.(10) It is also suggested that facilitative male partner responses will improve sexual functioning, whereas solicitous and negative responses may be detrimental for sexual functioning. Therefore psychological interventions that target partner responses may promote sexual rehabilitation.(11-12)

The data obtained, support our hypothesis that a multifaceted approach to PVD can lead to substantial improvements in vulvar pain and the resumption of intercourse. However, caution with intercourse is still warranted and even after treatment, intercourse continues to be a hypersensitive act in the majority of cases. It is essential to discuss this prior to treatment, preferably together with the partner. Not only the symptoms but also the treatment goals and results should be considered in the context of the mutual interaction in general and specifically while making love. At intake and prior to treatment realistic information should be given about the outcome of treatment, and patient education should also include possible changes in the couples' sexual repertoire.

Because of the retrospective design, lack of pre-treatment measurements and the absence of a control group, the outcome of this study should be considered as 'preliminary'. However, given the scarcity of research in the multidimensional approach these results may provide useful information for future prospective research efforts.

Before 2009 in our medical centre, vestibulectomy was the end-of-the-line treatment for otherwise therapy-resistant women. Success rates of vestibulectomy (in the short-term) in the literature varied from 61-94%, but 9% of the women reported increased pain at long-term follow-up.(13) From a medical perspective, high impact surgery is an ultima refuge, because it is irreversible and invasive. We therefore searched for a less intrusive treatment for PVD than vestibulectomy, to enhance the therapeutic power of our multidimensional approach.

Transcutaneous electrical nerve stimulation (TENS) has positive effects in chronic pain conditions and is non-invasive. As PVD is considered to be a chronic pain disorder, TENS might be a less radically therapeutic option than vestibulectomy for women with therapy-resistant vulvodynia. The therapeutic effect of TENS is most likely achieved by

inhibition of pain signals by stimulation of non-nociceptive afferent neurons (gate-control theory)(14) and by supraspinal inhibition.(15-17) As PVD is considered to be a chronic pain disorder, we introduced TENS as an additional treatment intervention for women with otherwise therapy-resistant PVD. We opted to apply TENS in a domiciliary protocol after giving the women comprehensive instruction, because this setting is patient-friendly, most likely cost-effective and the women are expected to be more relaxed in their home environment. The disadvantage of this domiciliary procedure is the impossibility to determine the exact compliance rate.

In line with what was discussed in **chapter 4** our feasibility study showed that the addition of self-administered TENS to multidimensional treatment significantly reduced the level of vulvar pain and considerably reduced the need for vestibulectomy. The beneficial effect on vulvar pain remained stable in the long-term (mean follow-up 10.1 months). Sexual functioning and sexual related personal stress improved significantly after administration of TENS as well. Whereas previously 23% of our serious treatment-resistant patient population ultimately underwent vestibulectomy(18), after the introduction of TENS this percentage fell to 4%. These results not only support the hypothesis that domiciliary TENS constitutes a feasible and beneficial addition to a multidimensional treatment for therapy-resistant PVD, but also that PVD can be considered a chronic pain syndrome. Researchers should realize that, placing the electrodes by the women herself could promote familiarity with the genital area, a non-intentional form of desensitisation, which in itself might have been therapeutic. In this study there was no control group. In future studies a transient sham TENS device could be used.(19)

PART II: PATHOPHYSIOLOGY

The second part of this thesis concerns the pathophysiology of provoked vestibulodynia. Although psychological 'inappropriateness' may be the key factor in understanding PVD, it is also interesting to study which physiological phenomena are involved, especially those which are considered to be 'involuntary'. The female reproductive system includes an active and responsive genital tract that shows involuntary activity that might be triggered by sexual arousal, genital stimulation and/or orgasm.(20-21) In this thesis, we explore whether reflex muscle activity ('genito-pelvic reflexes') might be an important constituent of the (dys)functional female sexual response.

First, in **chapter 5** we reviewed fifteen female genito-pelvic reflexes and their presumed sexual implications. At present, the literature on genito-pelvic reflexes and their sexual implications is very limited. It is speculated that these reflexes might be involved in the

sexual response; clitoral erection, milking semen from the male urethra during sexual intercourse, the tenting effect, sperm-ovum transport and possibly also in GPPPD. In several studies, it was also suggested that female genito-pelvic reflexes might play a role in preventing the leakage of faeces, flatus and urine during sexual intercourse.
However, the majority of studies on genito-pelvic reflexes have many methodological shortcomings. In addition, most of the studies are performed by the same research group and studies about the suggested sexual implications are not replicated by other groups. Therefore, the proposed sexual implications of the genito-pelvic reflexes reported in these studies have to be considered speculative.
More neurophysiological and sexological research is needed to confirm the presumed sexual implications of the genito-pelvic reflexes. We recommend that all the available studies are replicated according to current neurophysiological standards. More detailed information is required about the reflex arc, i.e. the receptors, afferent and efferent limbs, the integrative centre and effector(s). In addition, it would be worthwhile to investigate the brain areas involved in different genito-pelvic reflexes and to perform histological research in order to detect intravaginal receptors and their exact locations.

The anal, urethral and vaginal canals have a common embryonic origin. The vaginal canal is mainly considered as a canal for the passive passage of the penis, foetus, sperm and menses. Recent findings, however, suggest an active-responsive canal with pressure gradients.(20-22) Therefore, we evaluated whether the vaginal canal has its own sphincter-type mechanism in analogy with the anal- and urethral canals.
To shed more light on pelvic- and perineal contractions, in the study exposed in **chapter 6,** we performed intravaginal pressure measurements in 16 asymptomatic nulli-para women, using high solid-state circumferential catheters. In fifteen out of the sixteen women, two high-pressure zones were found, which indicates a deep and superficial contraction mechanism. These zones were generated by voluntary contractions and reflexive contractions. The pressures and the duration of the autonomic reflexive contractions significantly exceeded the pressures and duration of the voluntary contractions. The two high-pressures zones, as a result of voluntary contractions and, even more pronounced, as a result of reflexive contractions on intravaginal stimulation support our hypothesis that the vagina could have a sphincter-type mechanism. There were no significant differences between the reflexive measurements obtained in the left lateral recumbent to that in the sitting position. The preliminary data presented in this study will have to be validated in future studies.

Based on our findings in chapter 6, and also supported by findings from previous studies by others (23-24), we postulate the *genito-pelvic reflex hypothesis* in **chapter 7**. Until now, the role of genito-pelvic reflexes is almost ignored in sexual pain disorders. Our hypothesis is that vaginal contractions play an important role in the pathophysiology of the GPPPD. According to our genito-pelvic reflex hypothesis, in acute dyspareunia, women inadequately relax or contract their pelvic floor muscles (PFM), while continuing vaginal penetration despite pain. Voluntary pelvic floor muscle contractions or inadequate relaxation occurs to guard against pain due to vaginal trauma/infection and/or stress/anxiety. In chronic dyspareunia, these PFM contractions induce increasingly (sub) mucosal damage: contact- and pain receptors become more sensitive. This increased sensitivity of the contact receptors induces powerful autonomic reflexive contractions. These powerful autonomic reflexive contractions provoke vulvar pain, which causes overreactive PFM. In contrast to the voluntary system, the autonomic system is not triggered by pain and its contractions are more powerful than the voluntary contractions. Vulvar (sub)mucosal damage activates both the voluntary- and autonomic system and this occurs simultaneously, suggesting that these systems are connected. However, in essence these systems are not coupled. Therefore, the willingness to relax PFM does not affect the autonomic circle. In contrast to women with chronic dyspareunia/PVD, women with lifelong vaginismus are struggling with powerful autonomic reflexive contractions that dominate the entire disease process. This causes these women's inability to allow vaginal penetration.

More research is needed to test this genito-pelvic reflex hypothesis. A first step could be to measure vaginal reflexive contractions in sexually asymptomatic women under different conditions: at neutral-baseline, in response to negative emotions (e.g. disgust and threat) and most importantly, during exposure to erotic stimuli and disorder-specific stimuli (e.g. penile-vaginal penetration). Neurophysiological techniques are suitable means to analyse and describe the components of the reflex arc. Additionally, a histological approach is needed to detect the exact anatomical locations of the vaginal/vulvar receptors. In order to confirm the autonomic character of the reflexes, tests need to be replicated in different study groups under different circumstances, e.g. in asymptomatic women 1) under superficial anaesthesia and 2) under spinal anaesthesia and 3) in women with spinal cord lesions. In future research vaginal reflexive contraction tests should also be applied to clinical populations, in particular to women with lifelong vaginismus and chronic dyspareunia/PVD. Moreover, it is of major importance to evaluate the roles of different emotional stimuli on pelvic floor muscle contractions in healthy subjects and in women with vaginismus and dyspareunia to pursue the hypothesis of a link with the limbic system.

PART III: REFLECTION

In **chapter 8** we comment on the merging of vaginismus and dyspareunia into genito-pelvic pain/penetration disorder (GPPPD). This complicates the continuation of research on differences between lifelong vaginismus and dyspareunia/PVD. To be able to identify lifelong vaginismus within the GPPPD classification our proposal is to add an ad hoc specifier to the GPPPD to indicate that "vaginal intercourse has never been possible".
There are study results that show that women with vaginismus on levels of anxiety and avoidance behavior can be distinguished from women with dyspareunia.(25) Fear of pain can lead to avoidance behaviour. Fear, however, does not immediately have to be a result of pain. Avoidance of vaginal penetration can be the result of fear that is not directly related to the experience of pain and has a more phobic character.
Despite these two different forms of avoidance, avoidance is not a separate diagnostic criterion for GPPPD, while women with vaginismus precisely seem to distinguish from women with dyspareunia in their form of avoidance. In addition, better treatment outcome in lifelong vaginismus is associated with a reduction in fear and avoidance behavior, far more so than other treatment approaches.(26) With the introduction of GPPPD it is and still remains unclear whether it concerns a woman with a genital pain problem or a penetration phobia. Our second proposal is to state this contextual information explicitly in the diagnosis and/or inclusion criteria of scientific research.

REFERENCES

1. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.) Arlington, VA: Author
2. Cherner RA, Reissing ED. A comparative study of sexual function, behavior, and cognitions of women with lifelong vaginismus. Arch Sex Behav 2013;42:1605-1614.
3. Borg C, de Jong PJ, Weijmar Schultz WCM. Vaginismus and dyspareunia: automatic vs. deliberate disgust responsivity. J Sex Med 2010;7:2149-2157.
4. Meana M, Binik YM, Khalife S, Cohen D. Dyspareunia: Sexual dysfunction or pain syndrome? J Nerv Ment Dis 1997;185:561–9
5. Friedrich J. Vulvar vestibulitis syndrome. J Reprod Med 1987;32:110–4.
6. Ponte M, Klemperer E, Sahay A, Chren MM. Effects of vulvodynia on quality of life. J Am Acad Dermatol 2009;60:70–6.
7. Arnold LD, Bachmann GA, Rosen R, Kelly S, Rhoads GG. Vulvodynia: Characteristics and associations with comorbidities and quality of life. Obstet Gynecol 2006;107: 617–24.
8. Leo RJ, Dewani S. A systematic review of the utility of antidepressant pharmacotherapy in the treatment of vulvodynia pain. J Sex Med 2013;10:2498-2505.
9. Ben-David B, Friedman M. Gabapentin therapy for vulvodynia. Anesth Analg 1999;89:1459–60
10. Smith KB, Pukall CF. A systematic review of relationship adjustment and sexual satisfaction among women with provoked vestibulodynia. J Sex Res 2011;48:166-91.
11. Rosen NO, Bergeron S, Sadikaj G, Glowacka M, Delisle I, Baxter ML. Impact of male partner responses on sexual function in women with vulvodynia and their partners: a dyadic daily experience study.Health Psychol 2014;33:823-31.
12. Rosen NO, Bergeron S, Sadikaj G, Glowacka M, Baxter ML, Delisle I. Relationship satisfaction moderates the associations between male partner responses and depression in women with vulvodynia: a dyadic daily experience study. Pain 2014;155:1374-83.
13. Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI, Meana M, Amsel RA. A randomized comparison of group cognitive behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain 2001;91:297–306.
14. Melzack R, Wall PD. Painmechanisms:A new theory.Science 1965;150:971–9.
15. Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: Basic science mechanisms and clinical effectiveness. J Pain 2003;4:109–21.
16. Liebano RE, Rakel B, Vance CG, Walsh DM, Sluka KA. An investigation of the development of analgesic tolerance to TENS in humans. Pain 2011;152:335–42.
17. Melzack R, Wall P. Transcutaneous electrical nerve stimulation. In: Houston MJ, ed. Handbook of pain management. 1st edition. London: Elsevier limited; 2003:464–70.
18. Spoelstra, SK, Dijkstra, JR, van Driel, MF, & Weijmar Schultz, WCM. Long-term results of an individualized, multifaceted, and multidisciplinary therapeutic approach to provoked vestibulodynia. J Sex Med 2011;8:489–496.
19. Rakel B, et al. A new transient sham device allows for investigator blinding while delivering a true placebo treatment. J Pain 2010;11:230-238.
20. Levin RJ. Do women gain anything from coitus apart from pregnancy? Changes in the human female genital tract activated by coitus. J Sex Marit Ther 2003;29:59-69.
21. Ringrose CA. Pelvic reflex phenomena-incidence and significance. J Reprod Fertil 1966;12:161-165.
22. Broens PMA, Spoelstra SK, Weijmar Schultz WCM. Dynamic clinical measurements of voluntary vaginal contractions and autonomic vaginal reflexes. J Sex Med 2014;11:2966-2975.
23. Shafik A, El-Sibai O. Study of the pelvic floor muscles in vaginismus: a concept of pathogenesis. Eur J Obstet Gynecol Reprod Biol 2002;105:67-70.

24. Lahaie MA, Amsel R, Khalifé S, Boyer S, Faaborg-Andersen M, Binik YM. Can fear, pain, and muscle tension discriminate vaginismus from dyspareunia/Provoked vestibulodynia? Implications for the new DSM-5 diagnosis of genito-pelvic pain/penetration disorder. Arch Sex Behav. 2015;6-1547-1550.
25. Reissing ED, Binik YM, Khalife S, Cohen D, Amsel R. Vaginal spasm, pain, and behavior: an empirical investigation of the diagnosis of vaginismus. Arch Sex Behav 2004;33:5-17.
26. Ter Kuile MM, Melles R, de Groot HE, Tuijnman-Raasveld CC, van Lankveld JJ. Therapist-aided exposure for women with lifelong vaginismus: a randomized waiting-list control trial of efficacy. J Consult Clin Psychol. 2013;81:1127-1136.