DEEP DYSPAREUNIA: REVIEW OF PATHOPHYSIOLOGY AND PROPOSED FUTURE RESEARCH PRIORITIES

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Abstract

Introduction: Dyspareunia has been traditionally divided into superficial (introital) dyspareunia and deep dyspareunia (pain with deep penetration). While deep dyspareunia can co-exist with a variety of conditions, recent work in endometriosis has demonstrated that co-existence does not necessarily imply causation. Therefore, a re-consideration of the literature is required to clarify the pathophysiology of deep dyspareunia.

Aims: To review the pathophysiology of deep dyspareunia, and to propose future research priorities.

Methods: Narrative review after appraisal of published frameworks and literature search with the terms (dyspareunia AND endometriosis), (dyspareunia AND deep), (dyspareunia AND (pathophysiology OR etiology)).

Main Outcome Variable: Deep dyspareunia (present/absent or along a pain severity scale).

Results: Potential etiologies for deep dyspareunia include gynecological, urological, gastrointestinal, nervous system, psychological, and musculoskeletal system related. These etiologies can be classified according to anatomic mechanism (contact with a tender pouch of Douglas, uterus-cervix, bladder, or pelvic floor, with deep penetration). They can also be stratified into four categories (as previously proposed for endometriosis specifically), which can be utilized to personalize management: Type I (primarily gynecologic), Type II (non-gynecologic comorbid conditions), Type III (central sensitization and genito-pelvic pain

penetration disorder), and Type IV (mixed). Sociocultural and genetic factors and sexual response may also be important for deep dyspareunia.

Conclusion: We propose the following eight research priorities for deep dyspareunia: 1) development of deep dyspareunia measurement tools; 2) focus on the population who are avoiding intercourse due to deep dyspareunia; 3) clarification of the role of non-gynecologic comorbidities in the generation of deep dyspareunia; 4) addressing of ethnic and other sociocultural factors; 5) initiation of clinical trials with adequate power for deep dyspareunia outcomes; 6) inclusion of partner variables; 7) elucidation of pathways between psychological factors and deep dyspareunia; and 8) empirical validation of personalized approaches to deep dyspareunia.

Keywords

Deep dyspareunia; Superficial dyspareunia; Pathophysiology; Treatment

Introduction

Although sex should be a satisfying experience, the sad truth is that for too many women it is painful. Although the prevalence of sexual pain varies depending on study population and methods, one review showed that as many as 61% of women experience pain during sex in their lifetime [1]. This sexual pain can have a profound effect on a woman, her psychological well-being, relationships, and quality of life [2, 3]. Despite the wide spread prevalence of painful sex

among women, there is a need for more research to examine how and why this experience is so common.

Dyspareunia can be considered superficial (pain at the vaginal introitus with initial penetration) or deep (occurring within the pelvis in deep penetration) during penetrative intercourse. The etiology of superficial and deep dyspareunia are often different, with provoked vestibulodynia, pelvic floor dysfunction, vulvar dermatoses, and genitourinary syndrome of menopause being common causes of superficial pain. Similar to superficial dyspareunia, the causes of deep dyspareunia are heterogeneous and enigmatic. It is difficult to draw conclusions about deep dyspareunia from the current body literature because this type of pain is infrequently distinguished from superficial pain and is rarely a primary research outcome.

Deep dyspareunia is known to be important symptom in endometriosis and has been subject to some research [4]; however there is a need to consider other contributors to deep dyspareunia as well. In particular, it is important to note that simply because a condition co-exists with deep dyspareunia in the patient, does not necessarily mean that the condition is directly causing the sexual pain. The purpose of this review is therefore to re-consider the current evidence regarding the pathophysiology of deep dyspareunia within an anatomic model and a previously proposed framework for endometriosis specifically [5]. The framework uses pain mechanisms and the DSM-V concept of genito-pelvic pain penetration disorder to define four types of deep dyspareunia: gynecological (Type I), comorbid conditions (Type II), central sensitization and genito-pelvic pain penetration disorder (Type III), and mixed (Type IV) [5]. Furthermore, we aim to define a set of research priorities to guide the investigation of deep dyspareunia in the future.

Methods

For this narrative review, we examined both textbook frameworks for deep dyspareunia (e.g. [6]) as well as the published literature through PubMed search using the terms (endometriosis AND dyspareunia) OR (dyspareunia AND deep) OR (dyspareunia AND (pathophysiology OR etiology)). We did not include obvious anatomic causes of sexual pain, such as large fibroids or large ovarian cysts, which are dealt with surgically and are uncontroversial. In the Results, we specify "deep dyspareunia" when it was explicitly addressed in the cited study, but use the term "dyspareunia" when the study did not differentiate deep and superficial dyspareunia.

Results

ANATOMIC CONSIDERATIONS

It has been proposed that direct contact with a variety of tender pelvic structures at the apex of the vagina during deep penetration may be lead to deep dyspareunia [5]. These structures include: the pouch of Douglas/cul-de-sac, the cervix-uterus, the pelvic floor, and the bladder base [5]. This anatomic model will be considered below, under each of the four proposed Types of deep dyspareunia.

TYPE I: PRIMARY GYNECOLOGICAL CONDITIONS

Extrauterine (e.g. pouch of Douglas)

Endometriosis

Endometriosis is a common gynecologic condition characterized by ectopic uterine tissue that is classified as superficial peritoneal endometriosis (< 5 mm invasion), deep infiltrating endometriosis (≥5 mm invasion), or ovarian endometrioma (cysts). Approximately one in 10 reproductive-aged women are affected by endometriosis and half of these experience moderate to severe deep dyspareunia [7].

Deep infiltrating endometriotic lesions in the pouch of Douglas have been associated with deep dyspareunia likely because this area is contacted during penetration [8, 9]. Pelvic adhesions are common in endometriosis, especially with deep infiltrating endometriosis, and may also contribute to deep dyspareunia [10, 11]. With respect to superficial peritoneal endometriosis, one study showed that superficial endometriotic lesions of the pouch of Douglas in women with deep dyspareunia had increased density of nerve bundles, as well as elevated immune-intensity of nerve growth factor and its TrkA receptor, compared to patients with endometriotic lesions of the same anatomic location but without deep dyspareunia [12, 13]. These findings suggest that local neurogenesis around endometriosis may also contribute to pain with intercourse [12, 13]. Local inflammation via cyclooxygenase-2 (COX-2)–prostaglandin E2 (PGE2)–estrogen and other inflammatory positive feedback loops may also contribute to deep dyspareunia in endometriosis [14]. For example, in another study of women with deep infiltrating endometriosis of the recto-sigmoid colon, transforming growth factor beta (TGFβ), interleukin 7 (IL7), and interleukin 15 (IL15) were associated with severity of dyspareunia [15].

As discussed in a previous review on deep dyspareunia in endometriosis specifically, conventional treatments of endometriosis include hormonal suppression of the hypothalamic-pituitary-ovarian-uterine axis (with progestins, estrogen-progestins, or GnRH agonists) or surgical excision of lesions [5]. However, placebo-controlled randomized trials for these

conventional treatments have not shown a difference for the specific outcome of deep dyspareunia [5]. The reason for this may be related to inadequate power in these trials (as sexual pain is a secondary outcome only), or because of the increasing recognition of the multifactorial nature of endometriosis-associated pain that can include comorbid non-gynecologic conditions and central sensitization which require different management strategies (as discussed below). That being said, a placebo-controlled randomized controlled trial for a new oral GnRH antagonist for endometriosis showed a benefit for dyspareunia at higher doses [16], indicating that hormonal therapy may be beneficial in some cases. In addition, although not studied systematically, changes in sexual position that avoid contact with the pouch of Douglas (i.e. the posterior fornix of the vagina) may help reduce deep dyspareunia in the endometriosis population.

Genitourinary Syndrome of Menopause

Genitourinary syndrome of menopause (GSM) includes symptoms secondary to hypo-estrogenism during menopause with respect to the vulva, vagina, and lower urinary tract. Dyspareunia is a symptom of GSM that affects 44% of naturally or surgically postmenopausal women as well as women who experience estrogen deficiency as a result of chemotherapy or hormonal suppression [17-19]. To our knowledge, research studies on sexual pain in menopause have not distinguished superficial and deep dyspareunia; however, dryness, insufficient lubrication, and thinning of the vaginal epithelium, as well as shortening of the vagina due to diminished elasticity and flexibility, may contribute to deep pain at the vaginal apex such as at the pouch of Douglas [20, 21]. Conventional treatments include vaginal moisturizers, local

estrogen replacement, and newer hormonal therapies (e.g. prasterone and ospemifene) [22, 23], and although a complete appraisal of the literature of this topic is outside the scope of this review, it would be interesting to determine whether these treatments affect superficial dyspareunia and deep dyspareunia in the same way or differentially.

Iatrogenic

Shortening of the vagina, with sequelae similar to those of GSM, may occur after gynecological surgery or pelvic radiation [24-27]. Dyspareunia can sometimes arise de novo after hysterectomy; one prospective observational study showed that sexual pain was more common among women treated with vaginal hysterectomy than abdominal hysterectomy, perhaps because of shortening of the vagina in the former procedure [28, 29]. There is a lack of literature on studies evaluating strategies to manage surgically iatrogenic deep dyspareunia, although possibilities include local estrogen replacement and use of serial vaginal inserts [30-33]. In addition, impaired vaginal elasticity also appears to increase risk of deep dyspareunia following radiotherapy for gynecologic cancer. In a population-based study of women who received pelvic radiation, 40% reported deep dyspareunia and those with impaired vaginal elasticity were at greater risk of deep dyspareunia than those with normal vaginal elasticity [34].

Pelvic Organ Prolapse

Pelvic organ prolapse (POP) refers to the descent of the pelvic viscera due to weakness of the pelvic floor that can be described by compartment (anterior or cystocele, posterior or rectocele,

and apical). In a population-based study, 2.9% of women were found to have POP on physical examination [35]. The relationship between POP and dyspareunia is controversial; in a retrospective study Burrows et al. [36] found that 35% of women who had surgery for POP experienced sexual pain, whereas Handa et al. [37] found no association between POP and dyspareunia among women planned for hysterectomy. Notably, studies of dyspareunia in POP frequently use the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire [38] and the Female Sexual Function Index [39], which do not distinguish superficial and deep dyspareunia. Conceptually, any POP at the top of the vagina, such as a rectocele and/or apical prolapse at the pouch of Douglas, could contribute to the symptom of deep dyspareunia, and it would be interesting to know whether there is a difference between the compartments in producing the symptom of deep dyspareunia.

Treatment options for POP include pelvic floor physiotherapy, pessaries, and surgery. Previous research has not examined the effect of pessaries and pelvic floor physiotherapy on the specific outcome of deep dyspareunia, however these treatments are associated with increased frequency and satisfaction in sexual intercourse, and less inference of prolapse symptoms with sex life [38, 40, 41]. Minimally invasive or open repair for POP, with or without mesh, has not consistently been shown to decrease dyspareunia [42-45] and de novo dyspareunia after transvaginal mesh surgery may occur in a proportion of cases (4.5-27%) [46].

Uterus-cervix

Tu and As-Sanie have proposed a clinical diagnosis of “chronic uterine pain”, defined as pain in the midline deep pelvis (not caused by a non-uterine diagnosis), for 3 months, > 10 days/month,

and reproducible on uterine palpation on examination [47]. This clinical diagnosis is akin to the clinical diagnostic criteria for painful bladder syndrome and irritable bowel syndrome. Below are underlying diagnoses that could produce a tender uterus and chronic uterine pain. Although not evaluated in the literature, a possible strategy to reduce deep dyspareunia across these underlying diagnoses could be changes in position that avoid direct contact with the cervix-uterus.

Endometriosis

The uterine (eutopic) endometrium in endometriosis demonstrates local inflammation and estrogen production, as well as local neurogenesis, similar to what is seen in the ectopic lesions of endometriosis [14]. This uterine neuro-inflammation could lead to a tender uterus and to deep dyspareunia from contact with the cervix-uterus. Another potential mechanism is a restriction of mobility of the uterus due to endometriosis-associated adhesions (e.g. associated with deep infiltrating endometriosis), such that cervical-uterine contact during intercourse results in physical “pulling” on these adhesions.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) can manifest as endometritis, but also lead to salpingitis, oophoritis, and pelvic peritonitis, caused by the ascent of pathogens from the lower to the upper reproductive tract. Acute PID can lead to deep dyspareunia [48, 49]. Of more interest is chronic PID, which is listed as a cause of deep dyspareunia in multiple prior publications [50, 51].

However, there is little research into chronic PID and whether it really plays a role in persistent sexual pain. One study looking at the incidence of dyspareunia among Taiwanese women determined that female pelvic organ infections (i.e., PID) were a common cause of dyspareunia [52]. A previous randomized control trial found a decrease in abdominal and pelvic pain after short wave diathermy as a treatment for chronic PID; however, this study was limited by a small sample size and this is not a common treatment for PID [53]. To our knowledge there is no research that has established a mechanism linking chronic PID with deep dyspareunia or studied the effects of standard antibiotic treatment of acute PID on reducing risk of future deep dyspareunia.

Pelvic Congestion Syndrome

Pelvic congestion syndrome is a controversial entity characterized by the presence of ovarian vein reflux and peri-uterine pelvic varices [54]. This syndrome may be related to vasodilation as a result of increased estrogen [54, 55]. In a cohort of women with chronic pelvic pain, 31% had pelvic congestion syndrome, determined from pelvic exam, surgery, ultrasound, and venography [54, 55]. In the general population, the prevalence of ovarian varices was 9.9%, with more than half of those patients having clinical symptoms of pelvic congestion syndrome [54, 56]. Previous research found that 60.5% of a cohort of women with pelvic congestion syndrome (diagnosed by physical exam and/or ultrasound) had the symptom of dyspareunia, and additional studies identified dyspareunia and post-coital pain as common symptoms of pelvic congestion syndrome [54, 57, 58]. In another study, women with pelvic congestion syndrome had more dyspareunia compared to women with other pelvic pathology and compared to controls [59].

Treatment of pelvic congestion can include hormonal suppression, interventional radiology approaches to occlude the ovarian vein, or surgery. Women with pelvic congestion syndrome undergoing transcatheter foam sclerotherapy for treatment of pelvic varices reported a significant improvement in dyspareunia score 1, 3, 6 and 12 months after the procedure [57]. Ovarian and pelvic vein embolization also significantly reduced dyspareunia [54, 60]. While research is needed to differentiate between deep and superficial dyspareunia in these cases, it is more likely that pelvic congestion syndrome is related to uterine tenderness that leads to deep dyspareunia.

Fibroids

Estimates of the incidence of fibroids vary from 4.5% to 68.6% depending on study population and diagnostic methods; about a quarter of women with fibroids report deep dyspareunia [61, 62]. Women with uterine fibroids were shown to be 2.8 times as likely to report moderate or severe dyspareunia than women without fibroids [63]. Interestingly, there may be higher rates of dyspareunia among women with both a personal and family history of fibroids, compared to women without such a family history [64]. Dyspareunia has also been attributed to fibroids that fill the pelvis [65, 66], as well as cervical fibroids that result in bulk-related symptoms [51]. In contrast, a study by Moshesh et al. [62] showed that fibroid burden was not associated with degree of sexual pain.

Several studies have shown that deep dyspareunia was more associated with fundal fibroids than with fibroids in other locations, which might be explained by extreme anteversion or retroversion of the uterus bringing the fundus (and the fundal fibroid) up close to the vaginal apex where it can be contacted with deep penetration [51, 62, 63, 67]. In terms of treatment, myomectomy and

laparoscopic hysterectomy improved mean pain scores on the Female Sexual Function Index [68, 69] and women receiving medical or complementary interventions reported improved dyspareunia scores in one prospective study of women with symptomatic fibroids [70].

Uterine Position

Uterine retroversion can be congenital or acquired and manifests as the uterine fundus oriented towards the spine and posterior pelvis (pouch of Douglas). Approximately 20% of women have a retroverted uterus and it has been reported that up to two thirds experience sexual pain [71]. In a population-based study, Fauconnier et al. [71] found that women with uterine retroversion experience dyspareunia more frequently and with more severity than women with anteverted or intermediary (axial) uteri, suggesting a uterine retroversion can be causally related to painful sex. The mechanism driving dyspareunia in uterine retroversion may be related to penile collision with the uterus in the pouch of Douglas, or stretching of the uterosacral ligaments to accommodate the anterior shift of the cervix [71, 72]. That being said, there are many women with retroverted uteri that report no deep dyspareunia, suggesting other factors that may interact with a retroverted uterus to produce a tender uterus (e.g. local neuroinflammation). Observational studies have found that surgical suspension of the uterus significantly decreases dyspareunia among women with no significant pelvic pathology [73-75]; however, these results should be interpreted with caution until the efficacy of uterine suspension is confirmed in a randomized control trial [76].

Adenomyosis

Adenomyosis occurs when the endometrial cells that line the uterus are found in the myometrial layer of the uterus. In a large prospective study, Naftalin et al. [77] found that adenomyosis was present in almost 21% of women attending a general gynecological clinic. Notably, in 80% of cases adenomyosis was shown to coexist with other pelvic pathologies identified in this review [78], and to our knowledge no studies have examined the relationship between adenomyosis alone and deep dyspareunia. The contribution of adenomyosis to deep dyspareunia when other pathologies are present is unclear; for example Gonzales et al. [79] found that women with endometriosis and adenomyosis experienced more deep dyspareunia than women with endometriosis alone. In contrast, Ferrero et al. [80] showed that intensity of deep dyspareunia was the same across women who had bowel endometriosis with or without adenomyosis and that surgical intervention for endometriosis significantly reduced deep dyspareunia in all study groups.

TYPE II: CO-MORBID CONDITIONS

Deep dyspareunia may also be related to co-morbid non-gynecologic conditions including urological, gastrointestinal, and psychological conditions.

Urological

Interstitial cystitis/Painful bladder syndrome

Interstitial cystitis/painful bladder syndrome (IC/PBS) is pain, pressure, and/or discomfort perceived to be related to the urinary bladder, or worse with a full bladder, associated with

irritative symptoms in the absence of infection or other pathology, and may be a source of dyspareunia [58, 81, 82]. The prevalence of dyspareunia ranges from 49% to 90% in women with IC/PBS [10, 83-85]. In a study of women who underwent surgery for chronic pelvic pain, dyspareunia was found to be a risk factor for the diagnosis of IC [86]. In a prospectively recruited study of 47 women with confirmed diagnosis of IC/PBS according to the National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Disease, 32% of these women described their dyspareunia as unbearable and an additional 49% had some dyspareunia but still took part in sexual activity [87]. In a large cohort of women with and without IC/PBS, a greater proportion of women with IC/PBS reported dyspareunia compared to controls [88].

Presumably, dyspareunia in IC/PBS is related, at least in part, due contact with the bladder during intercourse (with another mechanism being the pelvic floor dysfunction seen in IC/PBS, as described below under musculoskeletal). Irritation of the bladder during sexual intercourse may also exacerbate the symptoms of IC/PBS [83, 89, 90]. In a cohort of women with endometriosis, our group has recently found an association between severity of deep dyspareunia and bladder/pelvic floor tenderness and a diagnosis of IC/PBS, controlling for endometriosis disease specific factors [91]. Tenderness of the bladder and pelvic floor, as well as the diagnosis of PBS, have been associated with deep dyspareunia in previous literature as well [92, 93]. It should also be emphasized that IC/PBS is associated with vulvodynia [94], and thus is also related to superficial dyspareunia.

A multidisciplinary treatment plan, including physiotherapy, bladder training, dietary modifications, as well as a combination of oral and intra-vesical instillation therapies, can be used to treat IC/PBS [89]. A previous study showed that treatment with 3 weeks of 3 times/week

bladder instillations resulted in improvement of dyspareunia among 57% of participants at their follow-up appointment [95]. However, prospective, randomized trials are needed. Changing sexual positions so as to avoid penile contact with the bladder may reduce some of the pain experienced during sexual intercourse in women with IC/PBS.

Recurrent urinary tract infection

Recurrent urinary tract infections (UTI) may also be associated with deep dyspareunia [66], again via penile contact with an inflamed bladder base. Salonia et al. [96] found that 44% of women with urinary incontinence and/or lower urinary tract symptoms suffered from dyspareunia or non-coital genital pain, and 61% of these also complained of recurrent bacterial cystitis. A population based study of women across the United States determined that presence of urinary tract symptoms was associated with a 7 fold increased likelihood of having sexual pain [97]. In both these studies, there is probably a mix of patients with IC/PBS and true recurrent UTIs. Women with recurrent UTI can report pain that is either superficial or deeper [96], which may be related to local inflammation or negative impact on lubrication, and treatment can improve sexual pain [96]. More research is needed in terms of the relationship between recurrent UTIs and deep versus superficial dyspareunia.

Gastrointestinal

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is characterized by gas, bloating, cramping, diarrhea and/or constipation. A meta-analysis of IBS in the community found that 14% of women meet the criteria for this condition [98] and 16.4% of women with IBS report dyspareunia [99]. Interestingly, the predominant constipation subtype of IBS is 2.38 times as common in women as men, and pain with intercourse is more common among women who have three or fewer bowel movements per week [100]. Pain with intercourse among women with IBS may result from collision of the penis with the constipated bowel that fills the pouch of Douglas, however the independence of the association between dyspareunia and IBS may require further scrutiny [91]. For example, after controlling for IC/PBS, one study did not observe an association between IBS and tender pelvic sites associated with deep dyspareunia [93].

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, varies significantly by geographic location and is as high as 23 cases per 100,000 person-years [101]. Between 18% and 40% of this population experiences painful penetration or intercourse [102], perhaps as a result of rectal inflammation and increased sensitivity in the adjacent pouch of Douglas, or in rare cases as a result of a fistula arising from the bowel that erodes into the vagina [103]. Dyspareunia in the IBD population is also related to IBS type symptoms, higher somatization scores, and perianal disease, but not with disease phenotype or other demographic factors [102, 104]. Increased dyspareunia may occur following surgical intervention [105], possibly as a result of altered anatomy or impacts on nervous supply that can reduce lubrication or vaginal proprioception [106]. It should be emphasized that IBD can also be associated with

superficial dyspareunia, such as via vulvar Crohn's lesions [107], and thus more work differentiating deep and superficial dyspareunia in this population is needed.

Psychological diagnoses

Depression and Anxiety

The majority of research on the relationship between psychological diagnoses and sexual pain is focused on superficial dyspareunia; however, evidence suggests that at least in the case of concurrent dyspareunia (patients with both superficial and deep dyspareunia), depression remains an important consideration [108].

There is a known relationship between sexual pain and depression/anxiety, focused primarily on superficial dyspareunia due to PVD [109-113]. Women with dyspareunia or provoked vestibulodynia (PVD) have been shown to have higher depression scores than controls, and depression is also associated with tenderness of the bladder and pelvic floor as well as a four times increased risk of vulvodynia [93, 109, 111]. Similarly, studies have shown that anxiety disorders are risk factors for sexual pain and that diagnosis of an anxiety disorder is ten times more common in women with PVD [109, 114, 115]. In one case-control study, the prevalence of depression and anxiety was significantly greater in women who reported dyspareunia symptoms compared to women without dyspareunia [116].

The direction of the relationship between psychopathology and sexual pain is likely bidirectional; depression and anxiety are considered both risk factors and consequences of PVD [115]. To our knowledge, no research has examined the impact of specific treatment for

depression or anxiety on deep dyspareunia, however caution is needed with drugs such as selective serotonin reuptake inhibitors given potential impact on sexual functioning. In contrast, psychotherapeutic approaches may work to reduce sexual pain: cognitive behavioural therapy and mindfulness are used in the treatment of depression and anxiety and are also effective in the treatment of PVD [115]. Further research is also needed in the potential role of psychological factors and their treatment in deep dyspareunia. In a recent published observational 1 year cohort for deep dyspareunia, a multidisciplinary approach including psychological therapies was associated with decreased deep dyspareunia at 1 year [117].

Musculoskeletal conditions

Myofascial pain syndrome

Myofascial pain syndrome arises from myofascial trigger points – exquisitely tender spots in taut bands of muscle. Myofascial pain and trigger points in the muscles of the pelvic floor is associated with dyspareunia [118, 119]; in one study dyspareunia was the presenting symptom among 47% of women receiving medical treatment of pelvic floor trigger points [120], and in another 86% endorsed deep dyspareunia [121]. Whereas superficial pain has been associated with dysfunction of the outer third of the vaginal musculature, deep dyspareunia has been attributed to trigger points on the posterior levator ani or obturator internus muscles [122], perhaps because these muscles are likely to be impacted with deeper penetration. Trigger points in deep pelvic floor muscles can refer pain sensation to the back, hips, and legs; this suggests that although deep dyspareunia occurs with deep penetration of the vagina, perception of the pain may not be limited to the vagina or even the pelvis [122].

Treatment for myofascial pelvic pain includes pelvic floor physiotherapy or injection of local anesthetics and/or Botox , both of which can significantly reduce dyspareunia [120, 121]. On the other hand, in a placebo controlled randomized trial, reduction in sexual pain did not differ between women treated with Botox versus saline injection [123] and a pilot randomized trial of physiotherapy versus injection with local anaesthetic and steroid showed that physiotherapy may be more efficacious in addressing deep dyspareunia [121].

A full discussion of vaginismus is outside the context of this review. However, a vaginistic response is likely to preclude penetration, and thus may be more a consideration for superficial dyspareunia, rather than deep dyspareunia.

TYPE III: GPPPD AND CENTRAL NERVOUS SYSTEM SENSITIZATION

In the DSM-V, genito-pelvic pain penetration disorder (GPPPD) is inclusive of both deep and superficial dyspareunia, and includes cases of dyspareunia not due to another medical condition (such as gynecological or non-gynecological diagnoses). We have previously proposed that in women with endometriosis, deep dyspareunia due to central nervous system sensitization may be related to GPPPD [5].

Central sensitization refers to the enhancement in the function of the neurons that results in an increased sensation of pain (hyperalgesia) or a sensation of pain from a non-painful stimulus (allodynia) [124]. Cross sensitization occurs when a pathologically painful organ/structure can lead to a non-painful organ/structure becoming painful [125-127]. This happens when non-painful afferent signals “jump the tract” and are processed through afferent pain pathways causing non-painful stimuli to be perceived as pain. In the literature, sensitization of the nervous

system is assessed through quantitative sensory testing (e.g., a lower pain-pressure threshold would indicate greater sensitization), brain magnetic resonance imaging (MRI), or the use of standardized questions for symptoms commonly seen in sensitized patients [124, 128]. Clinically, patients with central sensitization tend to have multiple pain diagnoses (e.g. fibromyalgia) and multiple body regions of pain, hyperalgesia, and allodynia.

Several studies have linked central sensitization and dyspareunia. In a study comparing women with dyspareunia to controls, women with dyspareunia had significantly lower pain pressure thresholds and a higher number of tender points, compared to controls [129]. Another study showed that among women with pelvic pain, intercourse pain was significantly associated with lower pressure thresholds at pelvic and extra-pelvic sites [130]. A study by Zhang et al., comparing women with superficial dyspareunia and healthy controls suggested that women with a longer history of superficial dyspareunia may be centrally sensitized [131]. In a study comparing women with superficial dyspareunia to healthy controls, a greater level of activation in the insula, dorsal mid-cingulate, posterior cingulate and thalamus was detected on fMRI during thumb stimulation in the women with pain [132]. In addition, As-Sanie et al. found that women with pelvic pain, with and without endometriosis, had decreased grey matter volume in left thalamus (a region in the brain involved in pain perception) [133].

Central sensitization may require a multidisciplinary approach. Pain adjuvants such as tricyclic antidepressants and trigger point injections have been studied in preliminary research, and psychological treatments like cognitive behavioural therapy and mindfulness based therapy have been suggested as another avenue for management [67, 124, 134]. Physiotherapy is also likely to be important; for example, women with superficial dyspareunia who underwent treatment with vaginal electromyographic feedback had a reduction of pain and could return to engaging in

intercourse [135]. In the recent published observational 1 year cohort for deep dyspareunia showing possible benefit for a multidisciplinary approach, pelvic physiotherapy was part of the multimodal treatment [117].

TYPE IV: MIXED

Type IV cases are those with multiple contributors to deep dyspareunia: whether gynecological, another comorbid condition, or central sensitization. An example would be the patient with known severe endometriosis (e.g. through ultrasound diagnosis of deep infiltrating endometriosis), who also has PBS/IC and evidence of central sensitization. It is not clear as to the ideal management of such patients. Surgically removing the gynecological pain stimulus could potentially reduce signaling to the central nervous system and reduce sensitization; on the other hand, surgery in a sensitized patient may worsen pain and result in a prolonged post-operative recovery. Alternatively, psychological or physiotherapy treatments could be utilized pre-operatively, and perhaps improve response to surgery, or even alleviate the deep dyspareunia and avoid the need for surgery altogether. This population of mixed etiology is deserving of more investigation.

SOCIOCULTURAL AND GENETIC FACTORS

Ethnicity appears to affect pain perception and reporting, which may be due to sociocultural factors or genetics. For example, studies using quantitative sensory testing have suggested ethnic differences in response to experimental pain stimuli [136-138]. The differences between

ethnicities may be attributed to social factors, such as socioeconomic status that may delay access to health care and thus contribute to increased severity of pain [139]. Another potential reason for discrepancies in pain between ethnicities may be genetics. Some women who have signs of central sensitization may have a genetic predisposition to autonomous pain amplification [140]. It has been suggested that people with chronic pain conditions have an impairment of endogenous inhibitory controls, which may be affected in part by genetic factors [125, 141]. It is possible these factors may vary by ethnicity, but at this point, any ethnic differences in the pathophysiology of deep dyspareunia severity are theoretical only.

Endometriosis is a common cause of deep dyspareunia and the genetics of endometriosis have been studied more intensively [142]. In the endometriosis literature, large-scale GWAS studies have identified approximately 12 loci associated with endometriosis risk, with these associations being stronger with more severe stage endometriosis. Recent work by our group has also identified somatic KRAS codon 12 mutations in the endometriosis epithelial cells in 26% of women with deep infiltrating endometriosis [143]. More invasive endometriosis of the pouch of Douglas is associated with more deep dyspareunia; thus, these genetic findings may play a role in the etiology and severity of deep dyspareunia.

There has not been much research on the genetics of dyspareunia specifically; however, recent studies looked at vulvar vestibulitis syndrome (PVD and superficial dyspareunia) have been reviewed [144]. A previous study by Heddini et al., determined that women carrying the 1438Gand 102C-alleles of the serotonin receptor gene (5HT-2A) had an elevated probability of having provoked vestibulodynia (which is a common type of dyspareunia) compared to healthy controls [145]. A study by Goldstein et al., found that women with vestibulodynia who were taking combined hormonal contraceptives were more likely to have longer cytosine-adenine-

guanine repeats in the androgen receptor, compared to women who did not develop vestibulodynia but took the same combined hormonal contraceptives [146]. Presence of allele 2 in the interleukin-1b gene was found to be more common in vulvar vestibulitis syndrome compared to healthy controls [147]. Finding that certain gene polymorphisms are more common in women with vulvodynia may allude to the presence of risk-associated polymorphisms in some women with deep dyspareunia; however, genetic research looking specifically at deep dyspareunia is required.

SEXUAL RESPONSE

The Basson Sexual Response Cycle (Figure 1) demonstrates that emotional intimacy, sexual stimuli, sexual arousal, and physical and emotional satisfaction affect female sexual response in a non-linear way [148]. Disruption at any point in the cycle can contribute to sexual pain. For example, a woman who has a persistent inability to obtain or sustain arousal may experience sexual discomfort as a result of reduced physiological response. Pain also begets pain (Figure 2); this has been borne out in classical conditioning experiments showing that pairing sexual stimuli with pain negatively affects sexual response [149]. As a consequence, dyspareunia is associated with several other aspects of sexual functioning such as vaginal dryness, difficulty reaching climax, and a lack of pleasurable sex [150]. It is important to note that research in this field either focuses on superficial dyspareunia or dyspareunia in general, and there is a need to empirically validate this model in deep dyspareunia [151] [152] (Figures 1-2).

The role of the sexual response cycle may be particularly important in women with pain catastrophizing cognitions. In particular, women who magnify, ruminate, or feel helpless about their deep dyspareunia may have a more amplified negative feedback response to their pain. Women with chronic pelvic pain have been shown to exhibit significant pain-related psychological involvement such as catastrophizing, fear and hypervigilance to pain during intercourse [130]. Another study demonstrated positive correlations between pain catastrophizing scores and dyspareunia [153].

RESEARCH PRIORITIES

There appear to be several promising avenues for exploration of the pathophysiology and treatment of deep dyspareunia. We consider the following to be important considerations for researchers investigating deep dyspareunia:

1) Measurement of Deep Dyspareunia

Only a minority of studies included in this review distinguished between deep dyspareunia and superficial dyspareunia. Given that there are often different causes, and therefore treatments, for these types of sexual pain, we recommend a focus on standardizing and validating a patient-reported measure for deep dyspareunia. This measure should consider recall period as previous research has found that asking women about dyspareunia in a recall period of more than one month resulted in a lower prevalence of sexual pain [51, 154]. In addition, an objective measure of deep dyspareunia requires development, analogous to the vulvalgesiometer or tampon test in PVD [155, 156].

2) Intercourse Avoidance

Across types of deep dyspareunia, researchers commented that a limitation of their research was the under-representation of intercourse-avoidant individuals (i.e., inclusion criteria were sexual activity, however patients with severe pain were often not currently sexually active and therefore excluded). Under-representation introduces bias potentially leading to the misrepresentation of treatment efficacy. We propose that women who abstain from sex due to pain should be included as a unique group in research.

3) Comorbidities

Many of the conditions described in this review frequently co-occur, thus it is difficult to establish causal relationships between any condition and deep dyspareunia. When studying the relationship between deep dyspareunia and particular condition, we recommend that researchers assess for other comorbidities, in order to control for confounding.

4) Sociodemographics

Difference in deep dyspareunia between ethnicities was not consistently reported in any of the reviewed studies despite research showing differences in pain perception and reporting between ethnicities [136-138]. We suggest stratifying study populations by ethnicity and acculturation to tease out differences between genetic, cultural, and economic factors. We also recommend study of LGBTQ individuals; in one study, the association between deep dyspareunia and sexual quality-of-life varied by sexual orientation [157].

5) Clinical Trials

Many studies we considered treated sexual pain as a secondary outcome, in particular randomized trials in endometriosis. We advise designing appropriately powered randomized control trials for sexual outcomes, in order to detect significant differences in deep dyspareunia in well-defined study populations, such as after treatment for endometriosis or IC/PBS.

6) Partner Variables

Of the reviewed papers, several mentioned partner characteristics as an uncontrolled factor that may affect dyspareunia. Male factors including phallus size as well as erectile and ejaculatory function may exacerbate deep dyspareunia. Moreover, relationship factors including level of trust and communication are likely to contribute to the self-management of sexual pain. Future research should examine the relationship between partner variables and deep dyspareunia.

7) Psychological Factors

A number of the reviewed articles identified psychological variables and sexual abuse as factors associated with sexual pain. The mechanisms underlying these relationships in deep dyspareunia, as well as the directionality of causation, both remain unclear. Therefore, we suggest studies examining the causality of these factors. For example, in a longitudinal prospective cohort, depression severity at baseline predicted worse deep dyspareunia at 1 year [117]. A clinical trial of depression treatment, with deep dyspareunia as the primary outcome, would be of particular interest.

8) Personalized treatment

The proposed framework in this review, whereby patients can be stratified by type of deep dyspareunia, requires further study for empirical validation. In addition to clinical trials of

treatments for conditions such as endometriosis and IC/PBS, there is a need for investigation of adjunct sexual health treatments specific to deep dyspareunia. This includes psychological and physiotherapy interventions, as well as spacers that limit depth of penetration and other self-management techniques (e.g., optimal positions for intercourse). Empirical validation of the sexual response cycle for deep dyspareunia is also needed, and sex therapy targeted to optimizing this cycle may be another treatment option in women with deep dyspareunia.

Conclusions

In this review, we described the pathophysiology of deep dyspareunia, as summarized in Figure 3, as well as potential treatments. Additionally, we proposed eight research priorities that highlighted the gaps in the existing literature about deep dyspareunia. In order for rigorous investigation of deep dyspareunia to proceed, researchers should develop and adopt valid measures of deep dyspareunia (patient-reported or objective). In future studies, special consideration should be given to the characteristics of study population including previously under-explored variables such as sociodemographics. Finally, clinical trials with adequate power for sexual pain are needed in deep dyspareunia.

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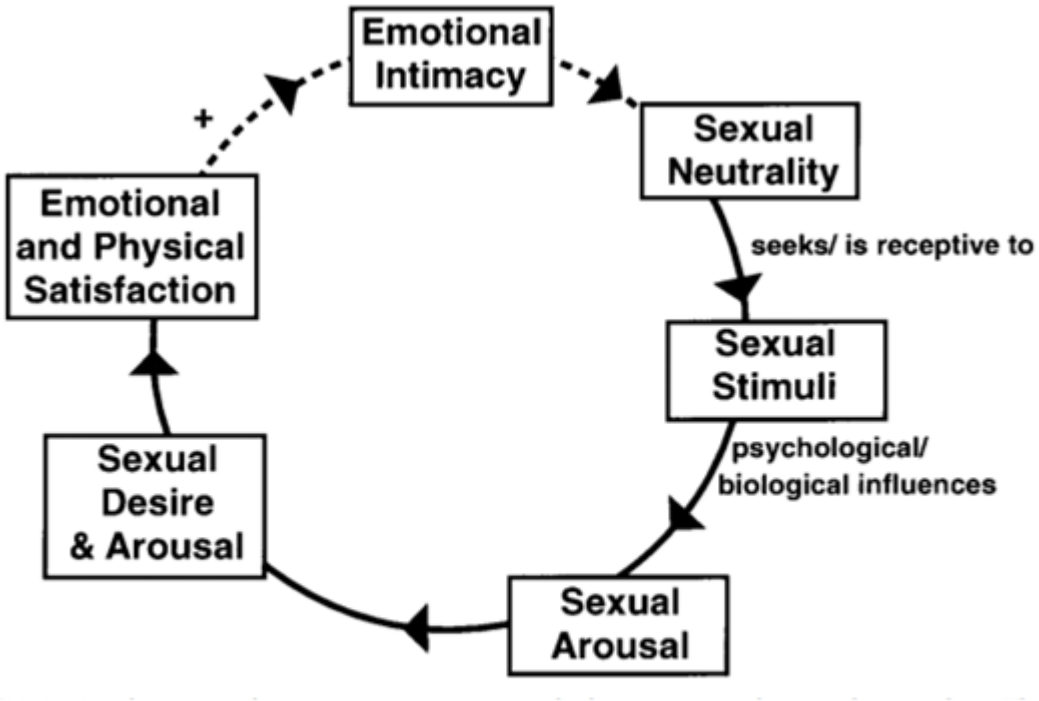

Figure 1. The Basson Female Sexual Response Cycle [151]. Copyright permission obtained from J Sex Marital Ther.

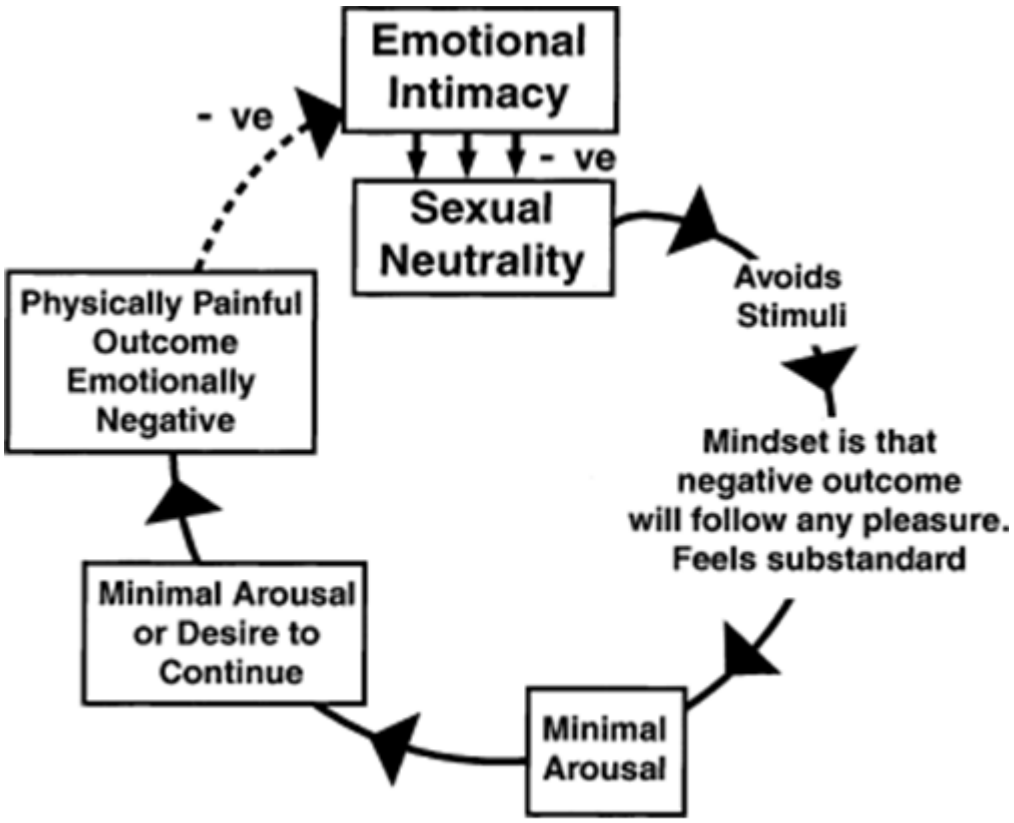

Figure 2. The effect of pain on the female sexual response cycle [152]. Copyright permission obtained from BJOG.

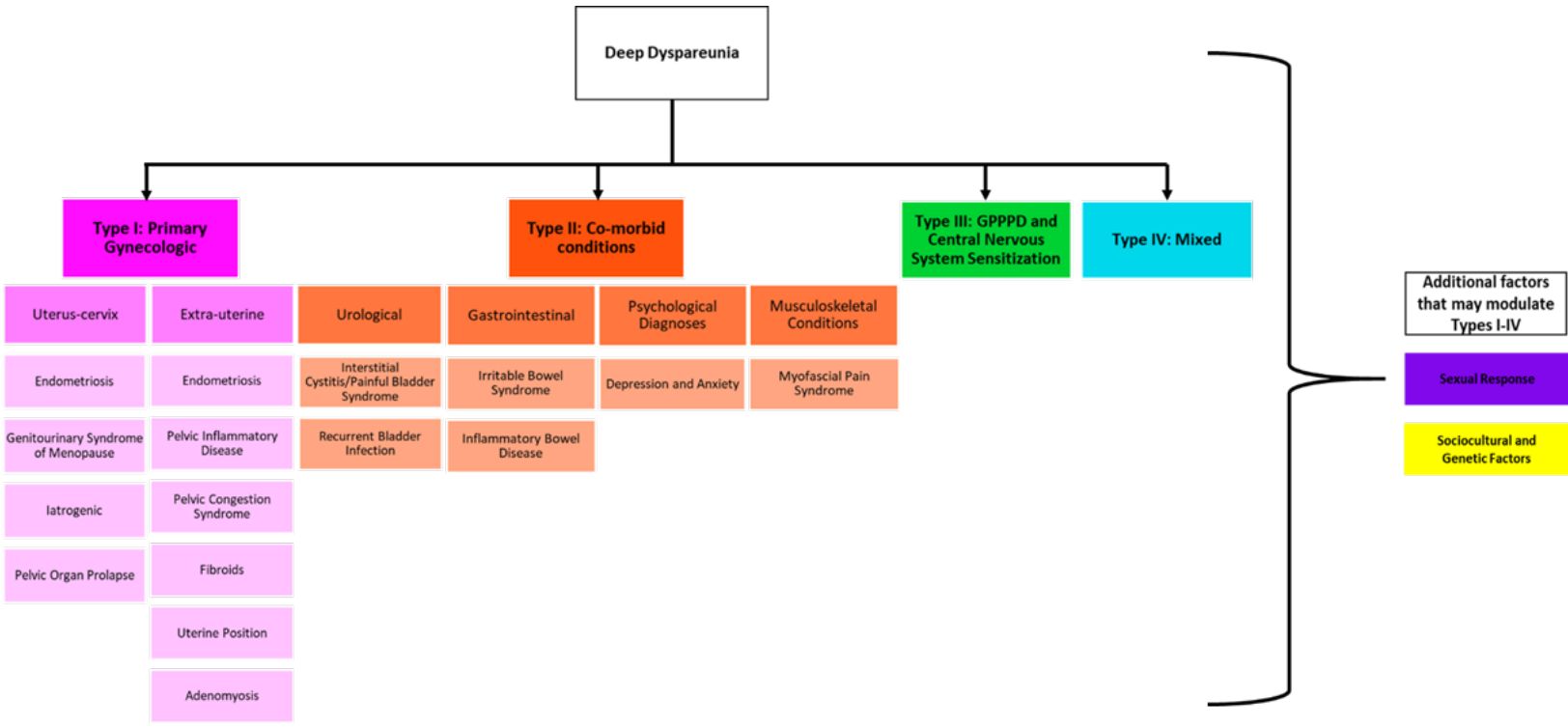

Figure 3. Summary of the types of deep dyspareunia.