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SYSTEMATIC REVIEW

Dyspareunia is rarely assessed in rodent models of endometriosis and interstitial cystitis/bladder pain syndrome

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Abstract

Dyspareunia, or pain during sex, is a common and often debilitating symptom in individuals with endometriosis and/or interstitial cystitis/bladder pain syndrome (IC/BPS). Despite its significant impact on quality of life, it is frequently overlooked in research. This review evaluates how dyspareunia has been addressed in preclinical investigations of these conditions. A systematic search was conducted using Embase from 1998 to 2021, identifying original *in vivo* preclinical studies using female rodents to model (i) endometriosis and (ii) IC/BPS. The search aimed to identify studies that assessed dyspareunia. Study quality and risk of bias were evaluated using a modified CAMARADES checklist. Our analysis found 1,286 studies modelling endometriosis and 674 modelling IC/BPS, but only 18 and 1, respectively, measured dyspareunia. The most common method involved vaginal distention in rats, assessed by either behavioural escape responses or visceromotor reflexes of abdominal muscles. Despite the high prevalence of dyspareunia in these conditions, it is rarely measured in preclinical studies. We identify a significant gap in the literature and offer succinct recommendations for future translational research to address this important symptom.

Lay summary

Dyspareunia describes pain occurring before, during or after sexual intercourse. This poorly understood symptom is particularly common in people suffering from two chronic pain-related conditions: endometriosis and IC/BPS, severely impacting their quality of life. Therefore, effective treatments addressing painful sex in people with these conditions are needed. To see the benefits of medical research at the patient's bedside, it is important to build from basic science research to preclinical animal studies then to human studies. Our study aims to assess the work that has been done so far at the 'preclinical' stage. Developments have been made in the methodology used to investigate this symptom in animals, and a summary of all the key findings may help build a platform to design future studies. Given the urgent need to develop new therapeutic strategies, attention given to painful sex by scientific medical researchers and physicians needs to improve.

Keywords: women's health; reproductive medicine

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Introduction

Dyspareunia refers to recurrent pain or discomfort occurring before, during or after sexual intercourse. An epidemiological study of sexually active women of reproductive age found that 41% reported dyspareunia (Zondervan *et al.* 2001). Despite its prevalence, dyspareunia remains poorly characterised and often neglected. It is often classified into superficial, with pain located at the external genitalia and vaginal opening, or deep, where pain is experienced with deep vaginal penetration. It is believed that different mechanisms underpin these types of dyspareunia (Tayyeb & Gupta 2024). Alternatively, it can be subdivided into primary (present from the onset of sexual activity) or secondary (arising after a period of pain-free sexual activity). Vulvodynia, 'a chronic sensation of pain, burning or rawness of vulval skin which cannot be ascribed to any specific cause and persists for at least 3 months', is distinct from dyspareunia (Bornstein *et al.* 2016). However, dyspareunia is a common symptom for those with both provoked and unprovoked vulval pain conditions (Hill & Taylor 2021).

Both men and women (and those who do not identify as either) can experience dyspareunia. Our interest here is only in those with female internal and/or external genitalia. We acknowledge that not all individuals with this anatomy identify as women, and conversely, not all women have this anatomy. However, the literature commonly uses the terms female/women without further clarification, and we adopt these terms for consistency. Dyspareunia in those with male genitalia, while not discussed here, is also under-researched and warrants attention in both basic and clinical studies (Luzzi & Law 2006).

Two indications associated with devastating chronic pelvic pain are endometriosis and interstitial cystitis/bladder pain syndrome (IC/BPS). Endometriosis is a chronic, hormone-dependent, inflammatory condition defined by the presence of tissue fragments similar to the endometrium outside the uterus. Endometriosis affects 6–10% of women of reproductive age (Huang *et al.* 2022) and up to 50% of infertile women (Meuleman *et al.* 2009). The condition's unclear aetiology and limited diagnostic options contribute to significant delays in diagnosis, and the need for the development of new, effective, non-hormonal treatments to manage chronic pain in endometriosis is increasingly recognised (Wheeler 1989, Rogers *et al.* 2009). People with endometriosis are at about nine times higher risk of deep dyspareunia than those without endometriosis (Ballard *et al.* 2008). Dyspareunia is one of the primary concerns affecting the quality of life of those with endometriosis (Hummelshoj *et al.* 2014), with 50% of symptomatic patients having impacted sexual activity and, in consequence, a negatively impacted quality of life (Bernuit *et al.* 2011, Demetriou *et al.* 2022).

IC/BPS is a chronic condition characterised by pain, pressure or discomfort related to the bladder, often accompanied by urinary symptoms such as frequency or urgency in the absence of other identifiable causes (Hanno & Dmochowski 2009). Its prevalence has been estimated to be between 2.7 and 6.5% of US women above 18 years of age (Berry *et al.* 2011). The diagnosis of IC/BPS is one of exclusion, leading to variability in clinical presentations. This, combined with the uncertainty surrounding pathophysiology, contributes to the low efficacy of existing treatments. In a study of women with IC/BPS, 61% reported dyspareunia (Lee *et al.* 2015). In addition, frequency of sexual intercourse and rates of desire and orgasm are significantly reduced, and fear of pain during sex increased in those with IC/BPS compared to disease-free controls (Peters *et al.* 2007, Gardella *et al.* 2011). The association between IC/BPS and deficits in sexual well-being is significant (Kim *et al.* 2019).

Pelvic pain conditions are generally comorbid, meaning that many patients will suffer with a combination of two or more of endometriosis, IC/BPS, irritable bowel syndrome and vulvodynia. The presence of comorbid endometriosis and IC/BPS is particularly associated with dyspareunia (Orr *et al.* 2018, Demetriou *et al.* 2022).

Valid and robust animal models are essential for translational research in dyspareunia associated with endometriosis and IC/BPS. To advance research in this area, it is crucial to have validated methods for assessing dyspareunia and reliable preclinical models of both conditions. However, most preclinical models of these conditions fail to assess nociception or pain, reducing their translational value by neglecting key disease components (Nunez-Badinez *et al.* 2021). In line with this, it is unclear to what extent dyspareunia has been studied in these preclinical models. To advance our disease understanding and to provide a platform for the evaluation of potential therapeutic compounds, it is crucial to understand the relationship between these conditions and dyspareunia.

This systematic review assesses the literature over the past 24 years (1998–2021) using rodent models of both endometriosis and IC/BPS in which dyspareunia has been measured. This analysis aims to contribute to the understanding of the methods used in this understudied area, with the ultimate aim of improving therapeutic options for patients suffering with endometriosis and/or IC/BPS-associated dyspareunia.

Materials and methods

Literature searches

This systematic literature review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page *et al.* 2021) and is

registered with the PROSPERO database (CRD42021271487). Searches were conducted on the Embase database (https://www.embase.com/#advancedSearch/default). Overall, two search strategies were defined, each designed to find relevant data on preclinical rodent models of endometriosis and IC/BPS, respectively. The advanced search settings included the following mapping options: 'map to preferred term in Emtree', 'search also as free text in all fields', 'explode using narrower Emtree terms' and 'search as broadly as possible'. The searches were limited to show results published between 01 January 1998 and 14 August 2021. The endometriosis search yielded 2,206 results, while the IC/BPS search yielded 943 results. These were exported into RIS (research information system) file format and imported into EndNote X8 (Clarivate, USA) for further analysis. Detailed search strategies are available in the supplementary material (see section on Supplementary materials given at the end of the article).

Study selection and data extraction

Only English-language articles were included. Screening was conducted in two phases: initial screening based on specific terms in the title and/or abstract, followed by full-text screening. Abstracts linked to published full-text articles were excluded, while those without were retained for full-text review. This decision was taken because we are reviewing a topic for which there is already limited research, so we wished to review all available data. Two reviewers (PN-B and RS) performed the screening phases for study selection independently and blinded to each other, following a previously agreed protocol that included predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion or consultation with a third investigator (KV).

Analysis of outcome measures and data synthesis

Two reviewers (PN-B and RS) independently extracted data, including species, age at intervention, outcome measures and frequency of measurements. Studies were sorted by publication date. The data format of the dyspareunia assessments was expressed as the number of observations in response to vaginal distention, such as muscle contractions or behavioural responses. The results focused on a description of the methodology and a narrative synthesis, a written summary of the aims and main results of the included studies. Due to insufficient data, no meta-analysis was performed.

Risk of bias assessment

The risk of bias of the included articles was assessed following a modified CAMARADES checklist for study quality (Macleod *et al.* 2004), omitting the parameter 'avoidance of an anaesthetic with intrinsic neuroprotective activities'. Recent studies have identified that all anaesthetics are likely to have a neuroprotective effect (Archer *et al.* 2018). Recent studies using the CAMARADES tool have similarly omitted this parameter (Cunningham *et al.* 2020, Kwak & Han 2020). Disagreements in quality assessment were resolved by consensus or arbitration by the correspondence authors (PN-B and RS).

Results

Study inclusion

A total of 2,206 and 943 potentially relevant search results for endometriosis and IC/BPS were identified, respectively (Fig. 1A). After removing duplicates, non-original research articles (e.g. reviews and editorials) and clinical studies (e.g. trials and case reports) were excluded. Then, all animal studies that were not performed *in vivo* (e.g. *in vitro*, *ex vivo* or *in silico* studies) or that were using animal species other than rodents were excluded. Next, all *in vivo* studies that were not investigating endometriosis or IC/BPS were excluded, yielding 1,286 and 674 *in vivo* studies, respectively. A full-text screening was performed to discard those studies in which dyspareunia was not included as an endpoint. In a final step, all conference abstracts that led to full-text publications were excluded, yielding 18 publications in which dyspareunia was measured in preclinical models of endometriosis (Fig. 1B) and one publication in an IC/BPS model (Fig. 1D), representing 1.5 and 0.1% of all included *in vivo* studies in these indications, respectively (Fig. 1C and E).

Study characteristics

The nineteen search results (18 from preclinical models of endometriosis and one from a preclinical model of IC/BPS) came from four research groups or collaborations, namely Berkley's group, which published 10 full-text articles and two abstracts; the Bayer/Evotec collaboration, which published one full-text article and three abstracts; Brierley's group, which published two full-text articles; and finally, Rodriguez's group, with one abstract (Table 1). From the eighteen studies measuring endometriosis-associated dyspareunia, 83% (15/18) used the autologous tissue in-transplantation model in Sprague–Dawley rats as a model for endometriosis and one publication used the allogeneic tissue in-transplantation model in mice (Castro *et al.* 2021).

Only one conference abstract reported the measurement of IC/BPS-associated dyspareunia (Rolston *et al.* 2018). Here, the water-avoidance-stress (WAS) model in

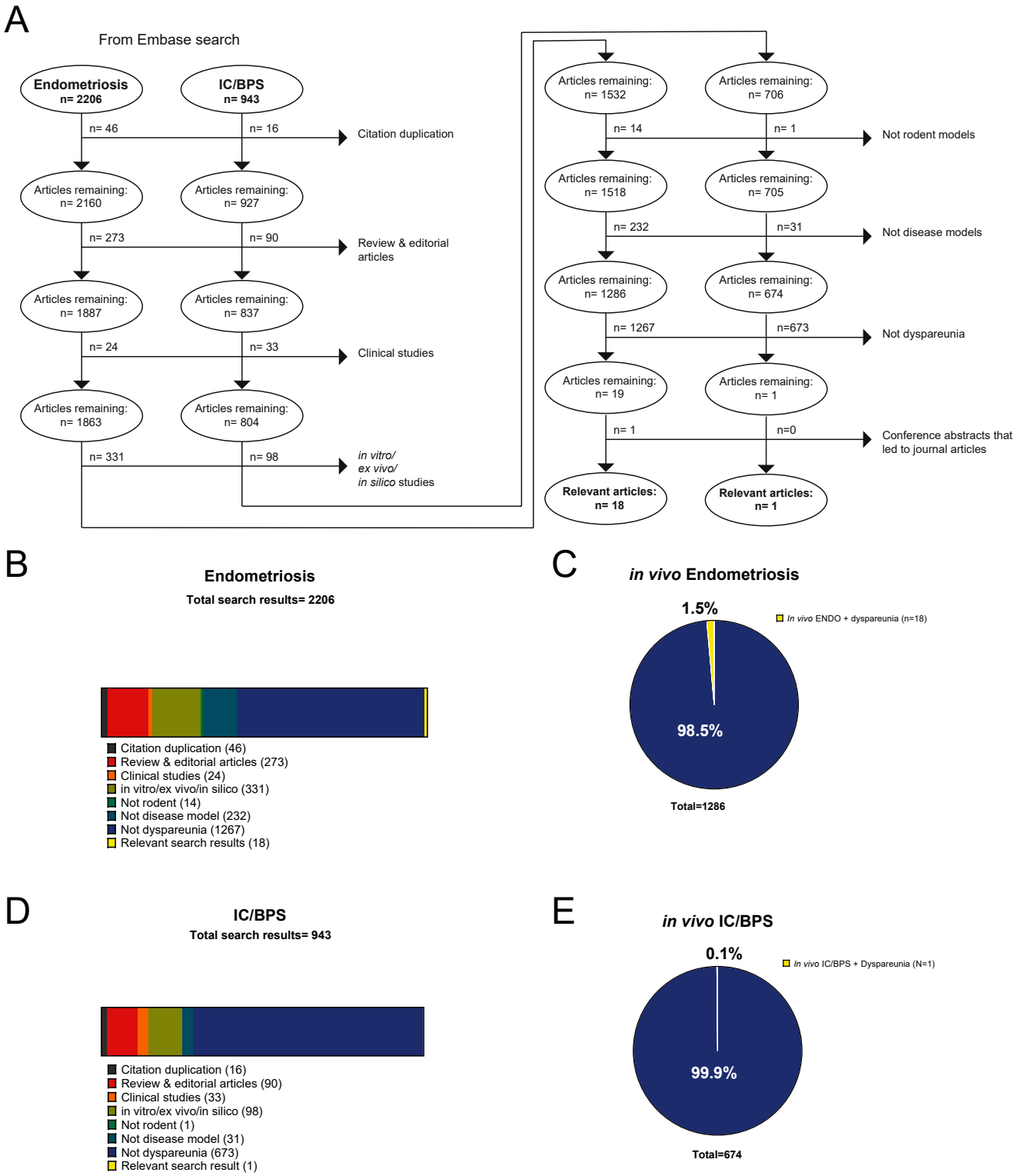

Figure 1

Systematic filtering strategy and selection of *in vivo* studies on endometriosis and IC/BPS assessing dyspareunia. (A) Flow chart of the systematic filtering of articles. (B and D) Distribution of search results for articles in endometriosis and IC/BPS, respectively. In black: citation duplication. In red: Review, Editorial articles. In orange: Clinical studies. In dark yellow: *in vitro/ex vivo* and *in silico* articles. In green: not rodent models. In light blue: not disease models. In blue: *in vivo* models of endometriosis and IC/BPS. In yellow: *in vivo* articles of the respective indications that included dyspareunia assessment. (C and E) Proportion of *in vivo* studies for endometriosis and IC/BPS that studied dyspareunia.

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Table 1 Characteristics of *in vivo* studies of endometriosis or IC/BPS that assessed dyspareunia. Search results were classified as follows: research group; reference type (original research article (OA) vs conference abstract); preclinical model of endometriosis or IC/BPS and species (autologous transplantation (AT) in Sprague–Dawley rats (SD), allogeneic transplantation (AL) in C57BL/6J mice or water avoidance stress (WAS) in Wistar rats); oestrus cycle stage of the animals at dyspareunia assessment; method (stimulus) of dyspareunia assessment (vaginal distention method (VD)); outcome measures (means to measure the degree of discomfort/pain that the stimulus elicited in the animals, pressure thresholds in millimetres of mercury (mmHg), behavioural escape responses or visceromotor reflex (VMR)); and time points of dyspareunia assessment in terms of weeks post-surgical induction of an endometriosis model. Assessments were done on a weekly basis.

Group	Study	Reference type	Model	Species	Oestrous cycle stage	Method/ stimulus	Outcome measures	Time points (weeks post-surgery)
Berkley	Berkley *et al.* (2001)	OA	AT	SD	N/s	VD	Pressure thresholds (mmHg) and escape responses	BL and 2–10
Berkley	Cason *et al.* (2003)	OA	AT	SD	All stages	VD	Pressure thresholds (mmHg) and escape responses	BL and 2–10
Berkley	Berkley *et al.* (2007)	OA	AT	SD	All stages	VD	Pressure thresholds (mmHg) and escape responses	BL and 2–10
Berkley	Nagabukuro & Berkley (2007)	OA	AT	SD	Proestrus or metoestrus	VD	VMR of the external oblique musculature and mean arterial pressure responses	~10
Berkley	McAllister *et al.* (2009)	OA	AT	SD	All stages	VD	Escape responses	BL, 4, 6–8 and 8
Berkley	Dmitrieva *et al.* (2010)	OA	AT	SD	Proestrus	VD	VMRth, mL	6–10
Berkley	Dmitrieva *et al.* (2012)	OA	AT	SD	All stages	VD	Telemetered VMR of the inguinal muscle	8
Berkley	McAllister *et al.* (2012)	OA	AT	SD	All stages	VD	Escape responses	BL and weekly 2–12
Berkley	Dmitrieva *et al.* (2014)	OA	AT	SD	Proestrus	VD	Telemetered VMR of the inguinal muscle	10–12
Bayer/Evotec	Hermann *et al.* (2015)	Abstract	AT	SD	N/s	VD	N/s	N/s
Berkley	McAllister *et al.* (2016)	OA	AT	SD	All stages	VD	Escape responses	BL, 1–4
Bayer/Evotec	Davenport *et al.* (2017)	Abstract	N/s	SD	N/s	VD	Number of abdominal contractions	N/s
Berkley	McAllister & Sinharoy (2018)	Abstract	AT	SD	Proestrus	N/s	N/s	BL, 6- and 8-week post-treatment
Berkley	McAllister *et al.* (2018)	Abstract	N/s	SD	N/s	N/s	N/s	N/s
Bayer/Evotec	De Leo *et al.* (2018)	Abstract	AT		N/s	VD	Number of abdominal contractions	5–6
Bayer/Evotec	Koppitz *et al.* (2019)	OA	AT	SD	Proestrus	VD	VMR of abdominal wall	5–6
Brierley	Ge *et al.* (2019)	OA	AT	SD	Proestrus	VD	VMR of the external oblique musculature	6
Brierley	Castro *et al.* (2021)	OA	AL	C57BL/6J	Proestrus	VD	VMR of abdominal contractions	6
Rodriguez	Rolston *et al.* (2018)	Abstract	WAS	Wistar rats	N/s	VD	VMR of the external oblique musculature	N/s

BL, baseline (before model induction); N/s, not specified; VMRth, VMR threshold.

female Wistar rats was used, and dyspareunia was assessed by measuring electromyographic activity of the external oblique muscle upon vaginal distention. This visceromotor (VMR) response was higher in the WAS model compared to control rats at all vaginal distention volumes. Authors concluded that increased vaginal sensitivity indicates that the WAS model of IC/BPS may be a suitable model of vaginal hyperalgesia/vulvodynia.

The vaginal distention method for the assessment of deep dyspareunia in *in vivo* rodent models of endometriosis

In 16/18 cases, dyspareunia was reported to be evaluated by the vaginal distention method. This method was first described in 2001 by Berkley and colleagues (Berkley *et al.* 2001), and it consisted of placing each animal in a testing

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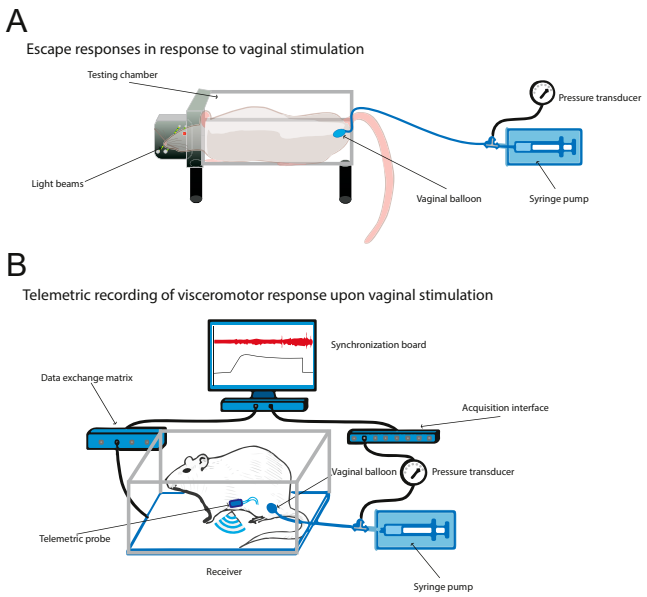

Figure 2

(A) Escape responses in response to vaginal stimulation. (B) Telemetric recording of visceromotor response upon vaginal stimulation.

apparatus consisting of a plexiglass chamber with a hollow tube equipped with light-emitting diodes and a photosensor (Fig. 2A). There, the vaginal canal of the animals was stimulated by inserting a latex balloon (10 mm length and 1.5 mm width uninflated). An automated pump inflated the balloon with water in steps of 1 μL to specified volumes for specified periods of time, and pressures generated by each distention were quantified using a small-volume pressure transducer. Animals were trained to detect and perform an escape behaviour upon noxious distention, and responses were quantified by head movements interrupting the light beam placed on the top of the chamber (Fig. 2A). The key finding from this first study – and the foundation for all research performed afterwards – was that endometriosis-induced animals tended to initiate escape behaviours at a lower magnitude of vaginal distention compared to sham animals (Berkley *et al.* 2001).

Important refinements of the vaginal distention model for a better understanding of endometriosis-associated dyspareunia

Since then, this method has been refined in terms of oestrus cycle phase at assessment, time of assessment after induction of an endometriosis model and technique to obtain the outcome measures (Table 1). These aspects are described below.

Berkley and coworkers found that dyspareunia levels correlated with oestradiol levels, being most severe during proestrus. In addition, vaginal hyperalgesia increased over a 2-month post-surgery period and then plateaued, which correlated with the presence of cystic lesions in the model. The authors concluded that the vaginal hyperalgesia depends upon the endometriotic cysts, as indicated for endometriosis patients (Kor *et al.* 2020). Due to the distance between cyst location and the vagina, the authors speculated that centrally mediated viscero-visceral interactions may be involved (Cason *et al.* 2003).

A subsequent study analysed the effects of reproductive senescence on endometriosis-induced vaginal hyperalgesia, finding that vaginal hyperalgesia correlated with oestradiol levels during reproductive senescence regardless of the presence of cysts, further supporting the idea that endometriosis-induced vaginal hyperalgesia is centrally mediated. In contrast, ovariectomy triggered a different type of vaginal hyperalgesia that does not affect endometriosis-driven vaginal hyperalgesia and oestradiol replacement alleviated it (Berkley *et al.* 2007).

Nagabukuro & Berkley identified that VMR and mean arterial pressure (pressor) responses could be used as an outcome measure for dyspareunia by considering how they are affected by vaginal distention. While distending the vaginal canal, they measured spikes of electrical activity through wires threaded into the external oblique musculature known to be a referred nociception known as the VMR response. Vaginal distention in surgically induced endometriosis rats increased the VMR and pressor responses greater than in the sham-surgery or the surgery naïve rats when assessed in proestrus. In the metoestrus phase, only the pressor response was significantly greater. This further supports that endometriosis is an oestrogen-dependent condition, as the increase in vaginal hyperalgesia was more pronounced in the more oestradiol-driven proestrus phase. Both VMR and pressor responses were found to parallel the behavioural escape responses to vaginal distention observed in previous studies. They concluded that investigations using escape responses as an outcome measure are time- and labour-intensive processes and that these alternative outcome measures could be more efficient strategies in future investigations. This study used urethane-anaesthetised rats, and another aim beyond this study was to develop the use of these outcome measures in awake rats (Nagabukuro & Berkley 2007).

McAllister and colleagues studied the effects of complete, partial and sham cyst removal in the model and found that while complete removal of endometrial cysts alleviated the vaginal hyperalgesia, partial and sham cyst removal increased it (McAllister *et al.* 2009). Moreover, the worsening of vaginal hyperalgesia due to sham cyst removal was associated with increased sympathetic innervation of the cysts, proposing this as a possible mechanism for increased

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endometriosis-induced vaginal hyperalgesia. In a follow-up study, the authors quantified the changes in cyst innervation over time parallel to behavioural assessment of dyspareunia (McAllister *et al.* 2012), finding that innervation starts to appear on the cysts at 2 weeks and fully matures at 6 weeks post-implantation. Moreover, abnormalities in sensory fibre function started 2–3 weeks post-implantation (McAllister *et al.* 2012). Levels of endometriosis-induced vaginal hyperalgesia positively correlated not only with cyst innervation density but also with vaginal canal sympathetic innervation density and prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) levels (McAllister *et al.* 2016). Finally, removal of cysts before acquiring functional innervation could prevent the occurrence of vaginal hyperalgesia. The authors concluded that sympathetic sensory coupling potentially underlies endometriosis-associated dyspareunia.

In addition, the same team used the endometriosis model to investigate possible treatment effects through the endocannabinoid system. They found that CB1 cannabinoid receptors were expressed on both the somata and fibres of both sensory and sympathetic neurons that innervate endometriotic lesions. Treatment with CB1 receptor agonists decreased, and treatment with CB1 receptor antagonists increased vaginal hyperalgesia. In this case, the VMR exceeded double the baseline value. The rats were contained in a testing box during assessment, and the wires threaded into their musculature were exteriorised out of the skin and attached to recording devices (Dmitrieva *et al.* 2010). The procedure to insert the testing wires was performed under anaesthesia 7–10 days in advance of the measurement of VMR, which was performed with the rats awake. Treating the animals with a CB1/CB2 agonist revealed an improvement in endometriosis-induced vaginal hyperalgesia and decreased the expression of vascular endothelial growth factor (VEGF) in the endometrial cysts, but not in the uterus. Altogether, the cannabinoid receptor signalling participates in the modulation of VEGF in the cysts, which in turn modulates vascularisation and/or innervation (McAllister & Sinharoy 2018). In addition, the group reported on the involvement of aldehyde metabolism in the modulation of endometriosis-associated vaginal hyperalgesia (McAllister *et al.* 2018).

Dmitrieva and colleagues further improved the use of VMR as an outcome measure by using telemetric probes for VMR assessment. In previous studies using VMR, the rats were tethered since the wires threaded into the musculature extended out of the skin and connected directly to the recording devices (Dmitrieva *et al.* 2010). In this study, a telemetric probe containing an electrode was implanted in the abdominal muscle. The electrode transmits electromyography signals via radiofrequency to a receiver located on the baseplate and connected to the acquisition module, which enables automatic and simpler data acquisition (Fig. 2B). The benefits of this technique included the rat no longer being tethered, issues of the exposed wires needing frequent repair being overcome, the rats being fully conscious and minimal training being required. The rat was still contained in a plexiglass box, and it was unclear whether this was any less restrictive than in previous studies. This assessment was conducted across oestrous phases and confirmed that the severity of vaginal hyperalgesia correlated with oestradiol levels as was found in previous studies. The team – in a collaborative effort with Bayer – also found that the cyclooxygenase inhibitor indomethacin increased the VMR threshold to vaginal distention, leading to less endometriosis-induced vaginal hyperalgesia (Dmitrieva *et al.* 2012). Anti-inflammatory compounds acted on vaginal hyperalgesia by decreasing the permeability of blood vessels in rat endometrial cysts (Dmitrieva *et al.* 2014).

Within a Bayer/Evotec collaboration, vaginal hyperalgesia was measured in endometriosis-induced rats at 5–6 weeks post-surgery. Vaginal hyperalgesia was characterised by an increased VMR in endometriosis animals compared to sham animals (De Leo *et al.* 2018). Furthermore, the group showed disease-modifying components on dyspareunia by treating the animals either with a P2X3 receptor antagonist or a microsomal PGE2 synthase (PTGES) inhibitor. Both compounds reduced endometriosis-induced vaginal hyperalgesia, which remained after 1 week of treatment-free period compared to vehicle-treated animals (De Leo *et al.* 2018).

Brierley's team also investigated the rat model of endometriosis-induced vaginal hyperalgesia and reported the beneficial effects of a guanylate cyclase-C (GC-C) agonist peptide, linaclotide (Ge *et al.* 2019). The authors observed a reduction in both vaginal hyperalgesia and in hind-paw mechanical allodynia. Interestingly, GC-C is not expressed in the vagina nor in the endometrial cysts, but the authors observed evidence of cross-organ interactions between the colon, vagina and ileum, supporting the idea that a viscero-visceral crosstalk between these organs participates in endometriosis-associated pain (Ge *et al.* 2019).

Recently, the same group has published a detailed characterisation of a murine autologous endometriosis model for over 10 weeks, including the assessment of vaginal hyperalgesia by vaginal distention 8 weeks post-surgery. Recording electrodes were surgically implanted at the external oblique abdominal muscle of mice, and the vaginal distention was performed on conscious animals after recovering from isoflurane anaesthesia using a balloon size of 3 mm and pressures in the range of 20–70 mmHg for 30 s (Castro *et al.* 2021). Mice with fully developed endometriosis have shown significantly increased VMR responses to vaginal distention pressures starting at 30 mmHg and up to the maximal pressure tested, 70 mmHg, compared to sham mice.

Analysis of study quality

The risk of bias and study quality were assessed using a modified nine-point CAMARADES checklist (Macleod *et al.* 2004). The quality of the included studies can broadly be considered of medium quality, with aspects that should have been included, although the description of methodology in full-text articles is robust. Of a maximum of nine points, the number of criteria met ranged from one to six, with a median score of four. The detailed assessment of study quality is reported in Table 2. The very low scores (one and two) were all generated from conference abstracts without a full-text publication, which would likely explain the failure to meet many criteria. In addition, many of these criteria were not regularly required at the time during which some of the full-text articles were published. It should be noted that this tool was developed in 2018–2019, so many of the publications it evaluates here predate its development. All included studies were peer-reviewed, and the majority reported the precise animal species used (84.2%) and stated compliance with animal welfare regulations (68.4%). Less than a third of studies mentioned control of temperature, reporting of excluded animals and whether the assessment was blinded to the experimenter. No study mentioned a power calculation for sample size, nor reported allocation concealment. Eleven studies did not report potential conflicts of interest.

Table 2 Risk of bias of the included studies. Studies filling the criteria are marked with an X for the respective criteria. Total defines the sum of fulfilled criteria.

	Criteria for assessment									
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
Berkley *et al.* (2001)	X			X	X	X		X		5
Cason *et al.* (2003)	X			X	X	X		X		5
Berkley *et al.* (2007)	X	X			X	X		X		5
Nagabukuro & Berkley (2007)	X			X		X		X		4
McAllister *et al.* (2009)	X	X			X	X		X	X	6
Dmitrieva *et al.* (2010)	X	X				X		X	X	5
Dmitrieva *et al.* (2012)	X					X		X	X	4
McAllister *et al.* (2012)	X	X				X		X	X	5
Dmitrieva *et al.* (2014)	X					X		X	X	3
Hermann *et al.* (2015)*	X									1
McAllister *et al.* (2016)	X	X			X	X		X	X	6
Davenport *et al.* (2017)*	X									1
McAllister & Sinharoy (2018)*	X									1
McAllister *et al.* (2018)*	X					X				2
De Leo *et al.* (2018)*	X					X				2
Koppitz *et al.* (2019)	X					X		X		3
Ge *et al.* (2019)	X	X			X	X		X	X	6
Castro *et al.* (2021)	X	X				X		X	X	5
Rolston *et al.* (2018)	X					X				2

*Conference abstracts. The criteria for assessment were as follows: 1, peer-reviewed publication; 2, control of temperature; 3, allocation concealment; 4, reporting of animals excluded from analysis; 5, blinded assessment to outcome; 6, precise animal species; 7, sample size calculation; 8, compliance with animal welfare regulations; and 9, statement of potential conflicts of interest.

Discussion

Despite the high incidence and prevalence of dyspareunia in endometriosis and IC/BPS patients, as well as the overwhelming personal and societal burden of this symptom (Facchin *et al.* 2021), this review clearly demonstrates the lack of preclinical research addressing this disorder. This, if unaddressed, will stunt the progression of understanding of this crucial symptom and limit opportunities to develop treatment options for this condition.

Overview of the methodology used to assess dyspareunia found in this systematic review

Dyspareunia in preclinical models of endometriosis and IC/BPS was only assessed by the vaginal distention method. The way in which the vaginal hyperalgesia induced by distention was measured was first developed by Berkley and colleagues (Berkley *et al.* 1995) and then replicated and/or refined over the years. First, behavioural escape responses in conscious animals were recorded and used as a readout for vaginal hyperalgesia upon increasing volumes of vaginal distention (Berkley *et al.* 2001). Later, this readout was replaced by VMR activity from abdominal muscles in anaesthetised animals (Nagabukuro & Berkley 2007). Later, the introduction of telemetric electrodes for VMR measurement (Dmitrieva *et al.* 2012) allowed for an automatic and simpler data acquisition procedure in conscious animals. Recently, Brierley and colleagues have developed a vaginal distention model in mice by downscaling the size of the balloon and pressures for vaginal distention (Castro *et al.* 2021). We believe this is a key improvement in the methodology, considering that it has been acknowledged that the syngeneic tissue in-transplantation model of endometriosis in mice possesses a higher construct validity for translational research than autologous transplantation models in rats (Nunez-Badinez *et al.* 2021).

The vaginal distention method, however, can only recapitulate deep dyspareunia. Our systematic assessment suggests that other forms of dyspareunia, including superficial dyspareunia and collision dyspareunia (where a retroverted uterus is directly knocked by deep penetration), have not been assessed in these models. This is a major limitation, highlighting the need for the development and assessment of new methodologies to assess them. This may be beyond the scope of application of a rodent model, due to their size and uterine anatomy and the potential relationship with other factors, such as arousal.

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Despite the high prevalence of dyspareunia in those suffering from IC/BPS, only one conference abstract was found, where dyspareunia was measured preclinically. Rodriguez and colleagues (Rolston *et al.* 2018) used the vaginal distention method in WAS-induced Wistar rats. The WAS model belongs to the 'stress-induced' category of model types for IC/BPS, one of three categories of model types used to study IC/BPS preclinically (Birder & Andersson 2018). Dyspareunia has not been studied yet in the other two categories: 'bladder-centric' and 'complex mechanisms'. Considering that IC/BPS patients may present with different aetiologies, this single result of one preclinical model category highlights the need for increased awareness and research on dyspareunia in preclinical models for this demanding condition.

No studies were found with a model of both endometriosis and IC/BPS in the same animal. This is particularly relevant because a diagnosis of IC/BPS is associated with more severe dyspareunia in those with all stages of endometriosis (Demetriou *et al.* 2022).

The disconnect between preclinical studies and clinical practice

Rodent models are widely used in preclinical investigations of both endometriosis and IC/BPS and aid in our understanding of the pathophysiology of these conditions, as well as finding approaches to treatment. An ideal preclinical rodent model should accurately reflect the whole human condition, including the spontaneous development of endometriosis or IC/BPS. In current models, the disease is induced by rather acute interventions to mimic the key characteristics of each condition, since the aetiologies of each condition are also not known (Birder & Andersson 2018, Burns *et al.* 2022). The results are numerous animal models that represent aspects of each condition and have individual applications in investigations. Selecting from a range of effective models to collectively create a picture resembling the pathology has shown limited success in replicating these conditions (Birder & Andersson 2018, Bruner-Tran *et al.* 2018), and the differences between these models and the true clinical situation are apparent.

The disconnect becomes more pronounced when the symptom in focus is dyspareunia. Attempting to model pain using preclinical models is not a challenge limited to endometriosis and IC/BPS. Animal models of pain depend on the method used to induce pain, the magnitude of chronic pain that can be modelled keeping in consideration the best possible animal welfare conditions (for example, severe non-escapable chronic spontaneous pain is not possible to model) and the mode of endpoint measurement, since different pathologies can be attributed to different behavioural measures in humans. For example, a pathology that causes pain at rest should be measured differently to an exertional pain. Therefore, animal research design should ideally encompass multiple outcome measures thought to best capture the clinical experience, such as resting pain, movement pain, hyperalgesia and quality-of-life measures (Gregory *et al.* 2013). Further to this, pain is a multidimensional experience, which encompasses physical, psychological, social and cultural factors that are subjective to the individual. These factors are arguably even more heavily weighted in the context of sex-related pain, making the preclinical modelling of sexual dysfunction all the more challenging (Marson *et al.* 2013).

From a clinical perspective, the presence of dyspareunia in patients may be associated with physical factors and/or medical conditions of different aetiologies. Therefore, the recommendation for practitioners is first to acknowledge and validate the patient's pain, identify and treat potential causes and then explore treatment options with the patient to best manage their symptoms (Sorensen *et al.* 2018). There are a wide variety of potential contributors to dyspareunia, including (but not limited to) vaginal atrophy, tension of the pelvic floor muscles and/or vaginismus, vaginal or pelvic infections, presence of a pelvic mass and scar tissue from previous injury to the vulva or vagina (including that related to childbirth). Whatever the initial cause is, there are likely to be secondary psychological or psychosexual factors that develop potentially, also leading to reduced arousal and lubrication even if desire is maintained. While basic scientists can identify potential mechanisms relating to disease induced dyspareunia, translation into successful clinical practice is likely to require a coordinated multi-disciplinary approach rather than purely a novel pharmacological therapy.

Study of dyspareunia in other preclinical research fields

A preclinical mouse model of vulvodynia, published in 2011 by Farmer and colleagues, might enable evaluation of other forms of dyspareunia (Farmer *et al.* 2011). Here, three model setups were evaluated: three repeated infections with *C. albicans* vs one long-lasting infection over 14 days vs two repeated zymosan (a mixture of fungal antigens) injections. Vulvar mechanical thresholds were evaluated using von Frey filaments. In all setups, some mice developed local vulvar allodynia. Particularly in the repeated *C. albicans* infection setup, the effect persisted over 32 days after the last infection round, long after the local infection had resolved. These mice also presented a dramatically increased vulvar innervation of both peptidergic sensory fibres and sympathetic innervation, which confirms the mechanisms in which allodynia is observed. Given that endometriosis and/or IC/BPS patients may also present with superficial dyspareunia, it is necessary to evaluate to which extent this model of superficial dyspareunia could

be incorporated into existing preclinical models of these indications.

The role of dyspareunia within the clinical picture of endometriosis and IC/BPS

The importance of prioritising dyspareunia within research of pelvic pain conditions cannot be understated. 'Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity' as defined by the WHO (The World Health Organization - Sexual and Reproductive Health and Research SRH 2015). The assurance of the highest attainable standard of sexual health is a protected human right. There must be recognition and improved understanding of the pathophysiological, social, psychological and interpersonal aspects that lead to the diminished sexual health experienced in both endometriosis and IC/BPS patients. In a recent manuscript from the TRiPP (Translational Research in Pelvic Pain) consortium, over 50% of people suffering from dyspareunia reported interrupting or avoiding sexual intercourse, while more than 30% across all diagnostic groups reported that their pain interferes with their sexual life (Demetriou *et al.* 2022).

While dyspareunia is a well-established symptom of endometriosis, its association with IC/BPS is perhaps less commonly thought about by clinicians. Patient partners, however, highlight the distress associated with this symptom and the associated impact on women's lives and their families. Dyspareunia can have a profoundly negative impact on the psychosocial and emotional well-being of patients. 'Sex is a normal part of the lives of human beings. If this form of intimacy is taken away, cracks may begin to appear in a relationship about which a patient may be very concerned and feel deeply guilty' (Meijlink 2023). Pain related to sex may cease when penetration finishes, but for many women, it can persist for many hours afterwards and even for some of those who do not find sex itself painful, it may be sufficient to trigger a flare in their other pelvic pain symptoms (Demetriou *et al.* 2022). In addition, for those with bladder symptoms, penetration may lead to an urgent need to void, thereby further disrupting sexual activity for both partners.

Currently, 'sexual health' in everyday practice is generally regarded as contraception services and testing for sexually transmitted infections. This is a very narrow interpretation of the field that is often separate from gynaecology, urology or pain services. Integrating sexual well-being into all areas of clinical practice can only be of benefit.

An important feature of the TRiPP consortium has been the involvement of patient partners from the outset. The relatively unique opportunity for preclinical scientists to receive direct feedback from patients into their work has improved the translational relevance of findings and allowed previously unconsidered areas, such as dyspareunia highlighted here, to be brought to the fore. We believe that encouraging this as a model for future work (as is now recommended by many funding bodies for clinical studies) will be key to breaking down barriers in translational research.

Conclusions and future perspectives

Herein, we have highlighted the paucity of preclinical investigations considering dyspareunia in the context of endometriosis and IC/BPS to date. The methodology to assess dyspareunia in rodents exists and has been developed over recent years to be less labour-intensive and has moved away from measurement of learnt behaviours towards measurement of autonomic responses, yet they are rarely used in combination with models of the clinical conditions associated with the symptom. Given the urgent need to better understand dyspareunia in women and to develop novel therapeutic strategies targeting this symptom, we believe this situation needs to change.

Based on our results, we propose the following recommendations: an assessment of dyspareunia should be applied to other preclinical disease models (e.g. syngeneic tissue in-transplantation models for endometriosis and 'bladder-centric' and 'complex mechanisms' for IC/BPS); in addition to deep dyspareunia, assessments of superficial dyspareunia should also be included in preclinical models of both diseases; and development of a rodent model of comorbid endometriosis and IC/BPS and combining this with assessments of pain, including dyspareunia, may have the highest translational benefit, given the poor quality of life associated with this clinical situation.

This review, alongside our previous work (Nunez-Badinez *et al.* 2021), has highlighted the need for researchers with expertise in disease models to collaborate with those skilled in pain assessments. In addition, we believe that close working with patient partners from the very start of project planning is essential to ensure that outcomes tested are those with the most direct benefit for future translational studies. We acknowledge that conversations about sex and intimacy are challenging; however, for our research (whether basic, clinical or translational) to have real benefits to patients, we need to address all areas that impact quality of life and that can only be achieved when we have a full understanding of the patient experience.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/RAF-23-0083.

Declaration of interest

All co-authors are members of the IMI-PainCare consortium. BDL, JN, NS and PN-B report personal fees from Bayer AG during the conduct of the study. BDL, JN and NS report personal fees from Bayer AG outside the submitted work. KV reports grants from the Innovative Medicines Initiative during the conduct of the study, grants and personal fees from Bayer AG, personal fees from Grünenthal GmBH, personal fees from Eli Lilly and personal fees from AbbVie outside the submitted work. JM, JB, LD and RS have nothing to disclose.

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Author contribution statement

KS and JN conceived the study. RS and PN-B reviewed the studies, analysed the data and drafted the manuscript. LD, BDL, JM, JB, NS, JN and KS edited the manuscript. KS and JN supervised the project.

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