Review

Experiences of Pelvic and Generalized Persistent Pain Syndromes in MRKH: A Scoping Review

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ABSTRACT

Study Objective: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is characterized by the congenital absence of the uterus and vagina, sometimes with associated extragenital anomalies. Currently, there is limited literature on pelvic pain and comorbid pain syndromes in people with MRKH. The aims of this scoping review were to summarize existing literature on pelvic and generalized persistent pain syndromes associated with MRKH and to identify knowledge gaps for further research into this field.
Methods: This scoping review followed the Joanna Briggs Institute framework. The population of interest was patients with a diagnosis of MRKH. MEDLINE, CINAHL, Scopus, Cochrane, Embase, and Emcare databases were searched. Articles that did not meet the inclusion criteria or critical appraisal standards were excluded. The resultant articles were reviewed by 2 independent researchers, and a third was used in cases of disagreement. A descriptive analytical method was used for data analysis.
Results: We screened 3348 articles for eligibility. Of these, 39 articles, which described 1353 cases of MRKH, met the criteria. Four studies described baseline pelvic pain in MRKH, 19 described acute presentations, and 13 described postintervention pain levels.
Conclusion: Despite the paucity of research, this review found that cyclic pelvic pain was mostly present in women with uterine remnants, whereas pelvic pain in those without remnants was poorly understood. There were no studies exploring generalized persistent pain syndromes in MRKH. Further cross-sectional studies are needed to elucidate the prevalence and levels of pain syndromes in MRKH.
Key Words: Uterine agenesis, Vaginal agenesis, MRKH, Pain, Pelvic pain, Fibromyalgia

Summary

This review summarizes existing literature on pelvic pain in women with MRKH, including sexual and postoperative pain. No studies have evaluated generalized pain syndromes in women with MRKH. Pelvic pain unrelated to obstructed uterine remnants in those with MRKH is poorly understood, and this review explores differential diagnoses to be considered.

Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (OMIM number 277000),[1] also known as vaginal, uterovaginal or Müllerian agenesis, is an uncommon congenital malformation with an incidence of 1 in 4000-5000 females.[2] MRKH varies between individuals; however, in most cases, it is characterized by the congenital absence of the uterus and vagina.[3] Some individuals with MRKH can have remnant uterine tissue lined with secretory endometrium.[5] Patients with MRKH can have associated extragenital manifestations including renal tract, cardiac, and skeletal anomalies (often classified as MRKH Type 2).[3,5] Throughout this review, the term "uterine agenesis" will be used to describe cases of patients without uterine remnants, and the term "MRKH" will be used to describe all other cases.

Patients with MRKH generally present in adolescence with primary amenorrhea, typical female secondary sexual characteristics, and a blind-ending or absent vagina.[4] Individuals with MRKH have a 46XX karyotype with normal ovarian function and hormone production. The diagnosis of MRKH is confirmed using clinical examination and ultrasound or magnetic resonance imaging but can also be reached after a diagnostic laparoscopy, showing uterovaginal aplasia or rudimentary Mullerian structures.[4] The relatively low prevalence and multiplicity of anatomical variants of Mullerian structures can make a diagnosis of MRKH challenging.[6]

Whereas studies have focused on functional outcomes including psychosocial well-being, sexual function, and sexual pain, there is a paucity of literature on experiences of nonsexual, pelvic, and generalized persistent pain syndromes in people with MRKH. Both pelvic pain and generalized persistent pain syndromes are significant health priorities that affect women disproportionately to men,[7,8]

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likely due to a myriad of psychosocial, hormonal, and sociocultural factors.[9] Menstruation is known to be a precipitator of pelvic pain in women without MRKH and has known associations with generalized persistent pain syndromes. Menstruation, the process of endometrial shedding, is also associated with exacerbations of inflammatory conditions due to cyclic prostaglandin and inflammatory mediator release.[10] Central sensitization, after repeated nociceptive stimulation, is known to be linked with persistent pelvic pain and is a key contributor to the development of generalized persistent pain syndromes (pain distributed over a large area of the body or found in multiple areas, often including fibromyalgia, migraines, or irritable bowel syndrome).[11,12] In women without MRKH, the role of hysterectomy in treating isolated pelvic pain has been described but is recognized to be less effective in women with generalized persistent pain syndromes and central sensitization.[13] Case reports of cyclic pelvic pain have been described in some patients with MRKH due to the presence of hematometra in obstructed uterine remnants with a functional secretory endometrium, encouraging the formation of adenomyosis and endometriosis from retrograde menstruation.[3,5,14-16] Although excision of obstructed uterine remnants appears to relieve acute pelvic pain, there is limited evidence regarding whether patients are likely to develop persistent pelvic pain and central sensitization after excision of uterine remnants. There are no previous reviews regarding central sensitization, fibromyalgia, or other generalized persistent pain syndromes in women with MRKH, and minimal data exist on the prevalence and experience of pelvic pain in most women with MRKH with uterine agenesis.

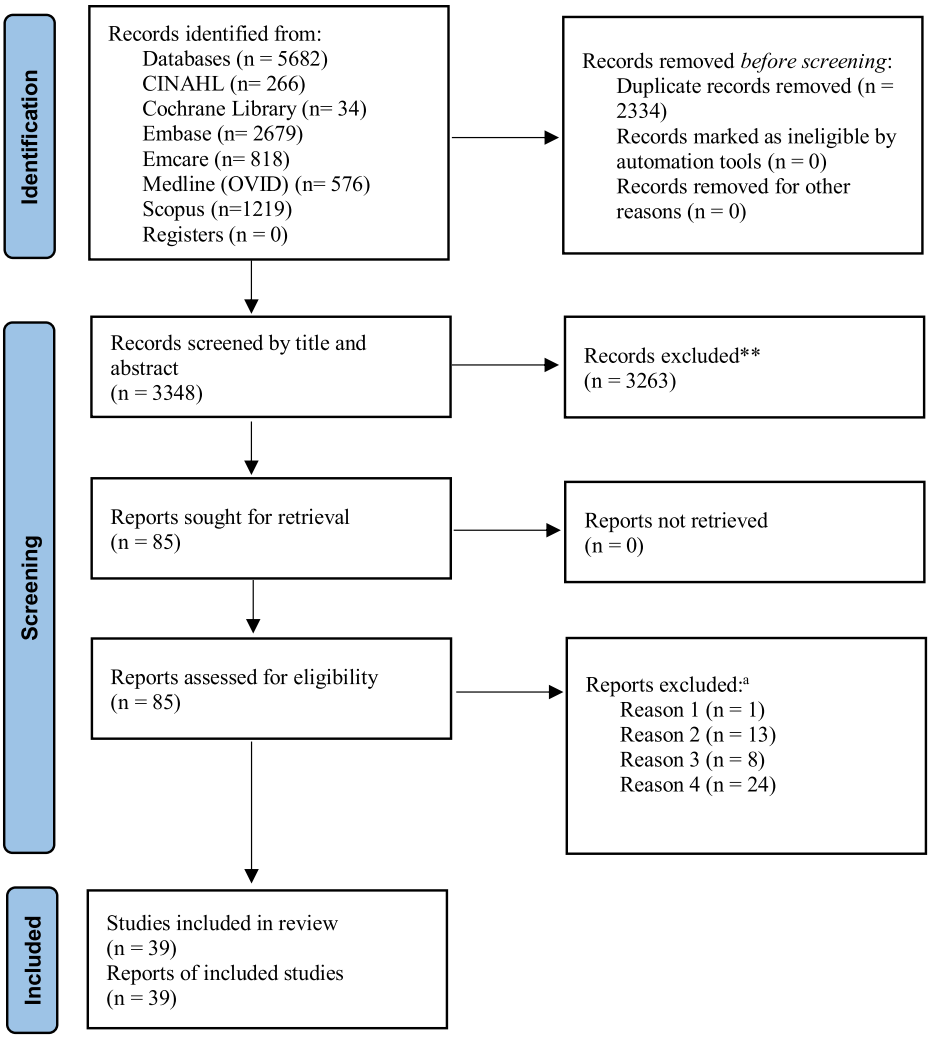
Despite a lack of evidence regarding pelvic pain and generalized persistent pain syndromes, several studies have focused specifically on sexual pain in women with MRKH. A recent systematic review explored dyspareunia and vaginismus after various methods of neovagina creation by using the Female Sexual Function Index (FSFI) and descriptive accounts.[17,18] The review included studies of patients who had undergone vaginal dilator use, the Vecchietti procedure, the Davydov procedure, Sheares' method of vaginoplasty, bowel vaginoplasty, and the use of full- and split-thickness flaps. The review found that the prevalence of dyspareunia was highest in the colovaginoplasty cohort (4.8%, 45 of 945 patients) and uniform among other cohorts.[17]

A scoping review allows for an understanding of the prevalence, etiology, and experiences of pain in patients with MRKH and the implications of different interventions and clinical phenotypes on pain levels and experiences. The aims of this scoping review were (1) to summarize the existing literature on pelvic and widespread pain in women with MRKH, (2) to map the current evidence on variations in pain with different interventions and clinical phenotypes associated with MRKH, and (3) to identify knowledge gaps and guide further research into pain syndromes in women with MRKH.

Materials and Methods

This scoping review followed the published methodology outlined by the Joanna Briggs Institute (JBI),[19] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension (Fig. 1) and checklist (Appendix 1) for scoping reviews[20] were used. The review protocol was developed a priori and is available on Open Science Framework: DOI 10.17605/OSF.IO/QEYSP. The initial search was implemented and updated between March and June 2022, using the databases MEDLINE, OVID, CINAHL, Emcare, Embase, and Cochrane. Search terms and subject headings are outlined in detail in Appendices 1-6. Descriptive observational studies, analytical observational studies, experimental study designs, secondary sources of evidence (including systematic reviews and meta-analyses), poster articles, video articles, and letters to the editor were included. The population of interest was patients with a diagnosis of MRKH meeting the American Society for Reproductive Medicine's 2021 Classification of Müllerian Anomalies[21]; of any age; with or without a remnant uterus; with pain of any character, location, and chronicity; and encountered in any health or community setting. No date limitations were applied. When articles were in foreign languages, English translations were obtained. Excluded were studies from which pain data for those with MRKH could not be extracted, studies that did not meet the American Society for Reproductive Medicine's 2021 diagnostic criteria for MRKH, and studies without descriptions of pain. Reference lists from the papers identified were reviewed to identify any additional papers missed in the initial search.

Title and abstract screening, followed by full-text review, was conducted by 2 independent researchers (RG and CP). A third reviewer (ND) was used in cases of disagreement. When articles could not be obtained through the authors' institutions' collections, attempts were made to retrieve them by contacting the authors directly. After full-text review, articles underwent critical appraisal, as described below. Data were then independently extracted by 2 researchers (RG and CP) from all included articles using a descriptive, analytical method. A standardized table was developed using the Joanna Briggs Institute Reviewers' Manual[19] as a guide to formulate data headings for data extraction from articles. Data headings included patient demographic characteristics—age at diagnosis and at time of intervention (if available), information about the study (including year of publication, country or countries of origin), study objectives, sample size, sites and features of pain, and the study methodology, including type of study, any intervention used and its description (including surgical procedures), intraoperative findings (including the presence or absence of rudimentary uterine remnants), use of pre- and/or postoperative vaginal dilation, length of the follow-up period, presence of postoperative pain, other outcomes of the study, and other key findings that related to the scoping review questions. Reports describing cases of dyspareunia, due to its overlap with pelvic pain, will be included in this review. Extracted data are available on request.



a= Reasons for report exclusion:

1. Unable to extract MRKH Syndrome pain data from wider populations.
2. Patients who do not meet the diagnostic criteria for MRKH Syndrome outlined in the ASRM's 2021 Classification of Mullerian Anomalies.
3. Does not describe any experiences of pain.
4. Excluded based on Critical Appraisal Tool.

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection depicts the process undertaken for study screening and selection for this scoping review. It also describes the reasons for study exclusion and the final number of studies included at each stage of the screening process.[20]

Case reports describing acute (<6 months) presentations of pain in people with MRKH were distinguished from those of patients who had persistent or recurrent pain when surveyed at baseline. Pain that occurred in cyclic patterns or was regularly repeated was denoted as cyclic pain. Cases of patients surveyed at their baseline who reported cyclic pain in the presence of a uterine remnant were reported under the cohort of patients

who had pain surveyed at their baselines. Contrastingly, patients who presented to health services with acute, isolated presentations of pain were grouped as case reports of acute presentations of pain in patients with MRKH.

Assessment of Methodological Quality and Risk of Bias

The JBI's critical appraisal tools were used to assess the methodological quality of the studies included.[22] This allows for the assessment of the risk of bias in a study's design, conduct, and analysis through the application of a consistent series of 8-12 questions (depending on the study type), to which the appraiser can use the answer boxes for "Yes," "No," "Unclear," and "Not applicable." All articles that met the inclusion criteria underwent critical appraisal by 2 reviewers (RG and CP), and a third reviewer (ND) was consulted to resolve disagreements. A decision was made among the members of the research team to exclude studies that yielded 3 or more "No" responses on the JBI critical appraisal tools, as these presented with a greater risk of bias in study methodology and conduct (Appendix 7), including a greater risk of selection and observation bias, as well as poor methodology.

Results

The database search yielded 5680 articles; 2334 articles were excluded as duplicates, and 2 additional articles were found through reference list searching, resulting in 3348 unique articles. After primary screening of titles and abstracts, 3263 articles were excluded for not meeting the inclusion criteria. Full-text review of the remaining 85 articles resulted in the exclusion of a further 46 articles on the basis of failure to meet the inclusion criteria or due to poor methodological quality through the critical appraisal process (Fig. 1).

After the review process, 39 articles remained, consisting of 1 review, 21 case reports, 6 retrospective case series, 7 cross-sectional studies, 2 cohort studies, and 2 case-control studies. The review article was not used for data extraction, as it described findings from articles that were already included for analysis. The dates of publication for articles spanned from 1992 to 2022. There were a total of 1353 cases of MRKH included in the review. Patients' ages ranged from 9 to 50 years, with an average age of 23.36 years. Patients' ages at diagnosis ranged from 1 to 46 years.

Pain Surveyed at Patients' Baselines

Of the included studies (n = 5), the focus was largely on pelvic pain in the setting of rudimentary uteri and associated complications secondary to hematometra, including endometriosis, adenomyosis, and endometriomas (Table 1). Presentations with pain led to a younger age of diagnosis of MRKH, as demonstrated in the study reporting 5 patients with pelvic pain presenting at a younger age (age range 9-18 years) compared with the 9 patients who presented for investigation of primary amenorrhea (age range 16-19 years).[23]

Most of the literature describing baseline pain recounted experiences of pain in women with obstructed uterine remnants, highlighting the paucity of studies describing experiences of pelvic and persistent pain in women without uterine remnants at their baselines. Marsh et al noted that 8 of 22 patients with MRKH reporting pelvic pain did not have uterine remnants, with pain in these patients reported to be either a singular episode of a self-resolving nature (5/8) or nongynecologic (gastrointestinal and musculoskeletal) pain (2/8).[16] The other experienced idiopathic recurrent cyclic pelvic pain. Among those without pelvic pain, 26 of 48 (54%), the proportion without uterine remnants was not reported. Sysak et al noted that half of their sample cohort did not have uterine remnants and that 5 of 16 (31%) presented with pelvic pain, although the reviewers were unable to elicit the presence or absence of remnant uteri among those with pelvic pain.[23] Baseline dysuria and dyspareunia were also reported in small numbers (3% each), although the presence of uterine remnants could not be elicited.[24]

Most patients with obstruction-related pain reported a cyclic pattern of pain.[16,23-25] The mean visual analog scale pain score was 6 (SD 2.1; range 0-9) among 34 women with pelvic pain who had MRKH with functional remnants, with most having associated endometriosis.[25] The pain was managed with excision of both the endometriotic lesions and the uterine remnants, and all patients were successfully discharged without persistence or recurrence of their pelvic pain.[25] A further study also found that patients with endometriosis and functional uterine structures reported a higher visual analog scale pain score of 6.2 (SD 1.8; range 0-9) than those without.[23]

Acute Presentations of Pain in Patients with MRKH

The etiology of acute pelvic pain presentations in women with MRKH varied among the included studies (n = 19 cases), from intrapelvic pathologies to nongynecologic and idiopathic causes (Table 2).

Of the patients presenting with endometriomas in the setting of MRKH, pain was largely acute,[14,26] with only 1 study reporting a patient with chronic pain.[27] Pain associated with endometriomas was mostly pelvic, with no associated systemic symptoms. Excision of the endometrioma, without excision of the rudimentary uterine tissue, allowed for alleviation of pain at follow-up in all cases, although the duration of follow-up was limited.[14,26,27] Similarly, patients presenting with leiomyomas presented mostly with acute pain in variable locations, and although excision of the affected uterine horn allowed for pain relief in 1 case,[28] the other 2 did not document postintervention pain status.[29,30] Pain associated with endometriosis was described as recurrent, persistent, and cyclic, with pain localizing to the pelvis.[31-33] Interestingly, endometriosis lesions were reported to be seen in 1 patient without a functional rudimentary remnant uterus, although in the absence of biopsy and histopathologic confirmation, this diagnosis is questionable.[31] The use of medical management, laparoscopic excision, and electrocautery was reported to be effective in reducing pain levels by follow-up.[31-33] However, the dura-

Table 1
Pain Surveyed at Patients' Baselines.

Study	Sample size	**Mean age** (range)/ *Range*/ **Mean age** (SD)	Location and features of pain	Presence/absence of uterine remnant(s)	Notes on cases
Marsh et al,[16]	48	**17.3**, *9-29*	No pelvic pain (26/48, 54%), pelvic pain (22/48, 46%), acyclic pain (8/22, 36%), cyclic pain (14/22, 64%)	In those with pelvic pain: - uterine remnant absent (8/22, 36%): nongynecologic pain (2/8, 25%), single episode (5/8), idiopathic (1/8) - uterine remnant present (14/22, 64%): with endometrium (9/14, 64%), without endometrium (5/14, 36%)	Authors attributed pain in those with a uterine remnant to the presumed presence of an obstructed remnant (9/14, 64%), unknown etiology (1/14, 7.1%), and spontaneously resolution (4/14, 29%). Pain was effectively managed with surgical removal of uteri and depot medroxyprogesterone acetate injections.
Dabi et al,[5]	21	**18.9** (SD 4.8)	Chronic pelvic pain (20, 95%), cyclic pain (16, 76%)	Unilateral uterine horn remnant (1/21, 5%), bilateral uterine horn remnant (20/21, 95%)	Intervention: surgical removal of the rudimentary uterine horn (14/21, 67%), myomectomy/cystectomy/peritoneal resection (6/21, 29%) Postoperative pain levels: No residual pain (7/14, 50%), residual pain present (3/14, 21%), missing information (4/14, 29%) Intraoperative findings: ovarian cyst (2/14, 14%), uterine myoma (4/14, 29%), peritoneal endometriosis (8/14, 57.14%).
Schall et al,[24]	33	*0-17*	No pelvic pain (26/33, 78.8%), pelvic pain (7/33, 21.2%)	Not reported	Other types of pain reported: cyclic pain (1/33, 3%), dysuria (1/33, 3%), dyspareunia (1/33, 3%)
Sysak et al,[23]	16	**16.75**, *9-20*	Not reported	Uterine remnants absent (8/16, 50%), fibrous band (4/16, 25%), rudimentary uterus present in (4/16, 25%)	Frequent clinical manifestations of MRKH syndrome: primary amenorrhea (9/16, 56%), pelvic pain (5/16, 31%) (age range for pelvic pain 9-18 years)
Tian et al,[25]	34	**15** (SD 3.5)	Pelvic pain (34/34, 100%), cyclic (30/34, 88%), acyclic (4/34, 12%)	Bilateral (34/34, 100%): 2 functional remnants (11/34, 32%), left functional remnant (14/34, 41%), right functional remnant (9/34, 27%)	Mean VASPS 6 (SD 2.1) (range 0-9), VASPS with endometriosis 6.2 (SD 1.8) Concurrent endometriosis (23/34, 68%),* concurrent endometrioma (15/34, 44%), concurrent adenomyosis (4/34, 12%), superficial peritoneal endometriosis (9/34, 26%)

MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; VASPS, visual analog scale pain score.
* After excision of endometriosis lesions and removal of uterine remnant (if present), none of these patients reported recurrent pelvic pain or recurrence of endometriosis at follow-up.

tion of follow-up was limited, and 1 patient returned with a further episode of pain.[31] Ovarian torsion, presenting with unilateral pain, occurred mostly in younger patients with MRKH and was the only pain presentation in the cohort of younger patients.[4,34,35] In 1 case of ovarian torsion, severe recurrent pelvic pain was reported, attributed to a longer-term torsion of the ovary with necrotic appearance laparoscopically.[35]

A unique presentation with refractory idiopathic infraumbilical pain that radiated to the back and perineum was effectively treated using a series of 3 superior hypogastric plexus blocks and an injection of a gonadotropin-releasing hormone agonist.[36] In this case, there was no remnant uterine horn, and the response to the gonadotropin-releasing hormone agonist suggests a possible association with ovulation.

Pain Experiences after Vaginoplasty and/or Vaginal Dilation

All studies reporting on postintervention pain (n = 13) reviewed postoperative pain, perineal pain, and/or dyspareunia after surgical vaginoplasty or vaginal dilation, and a wide array of objective and subjective methods were used to classify and record pain after intervention (Table 3). The FSFI,[18] a multidimensional survey for assessing sexual function in women, measures, among other symptoms, the presence of dyspareunia and vaginismus, with scores for pain ranging from 0 to 6 or 0 to 15, with higher scores indicating lower levels of pain during intercourse.[18] Baseline levels of sexual pain in a cohort of 24 women without MRKH (ie, a control cohort) were reported at 4.3 ± 1.5 (0-6).[42] Higher pain scores on the FSFI were associated with the use of intercourse as a method of vaginal dilation, as opposed to surgery or vaginal dilators. Among the surgeries reported in this study, the authors reported that sigmoid vaginoplasty was associated with significantly more dyspareunia and vaginal stenosis,[43] whereas another study showed that post-dilation FSFI scores were lower in this cohort compared with patients who underwent a laparoscopic Davidov procedure.[44] Of the 40 patients who underwent neovagina creation using the McIndoe vaginoplasty method, 17 reported being sexually active in the postoperative period, among whom 12 patients were regular mold users. Within this cohort, 6 reported no dyspareunia, 5 reported mild dyspareunia, and 1 had severe dyspareunia.[2] Of the remaining 4 sexually active patients, who were irregular postoperative vaginal mold users, 3 reported severe dyspareunia, and 1 reported mild dyspareunia.[2] Among the other surgical neovaginoplasties, superficial dyspareunia was reported in 20% of patients who were

Table 2
Case Reports of Acute Presentations of Pain in Patients with MRKH.

Diagnosis*	Age	Location and features of pain | Associated symptoms	Presence of uterine remnant	Management/Interventions	Postintervention pain levels
Urethral coitus (1)[39]	24	RLLQ, dyspareunia, partially relieved by analgesics | Sexual dysfunction, urinary incontinence	Present, singular (n = 1)	McIndoe vaginoplasty	Improvement at 6 months (n = 1)
Endometrioma (3)[14,26,27]	26	LLQ, acute (n = 3) | Nil (n = 3)	Absent (n = 1); present (n = 2)	Excision of endometrioma (n = 3)†; adjunct continuous combined low-dose monophasic oral contraceptives (n = 1)	No pain on follow-up at 1 month (n = 3)
Leiomyoma (3)[28-30]	16	Diffuse, chronic, acyclic, colicky, partially relieved by analgesics | Nil	Present, bilateral (n = 3)	Laparotomic excision of unilateral rudimentary horn with leiomyoma (n = 1), + unilateral salpingo-oophorectomy (n = 1); no intervention (n = 1)	No pain on follow-up at 1 month (n=2); pain levels not measured postoperatively (n = 1)
	40	RLQ, acute, sharp | Chills, decreased appetite, nausea, emesis‡			
	50	RLLQ, acute, sharp, not relieved by analgesics | Nil			
Adenomyosis (2)[6,38]	27	LLQ, recurrent (monthly), chronic| Nil	Present, bilateral (n = 2)	Gonadotropin-releasing hormone agonist (n = 1); laparoscopic removal of unilateral rudimentary uterine horn (n = 2), + bilateral salpingo-oophorectomy (n = 1)	No pain on discharge (n = 1)
	37	RLLQ, dyspareunia, chronic, worsening acyclic, not relieved by analgesics | Intermittent urine flow			No symptoms on follow-up at >1 month (n = 1)
Subhepatic Müllerian remnant cyst (1)[40]	17	RUQ, RLQ, acute, rapid onset, constant, sharp, cramping | Constipation, bilious emesis, anorexia	Not reported	Laparoscopic excision of subhepatic Müllerian cyst remnant	No pain on follow-up at <1 month after surgery
Endometriosis (3)[31-33]	20, 40, 27	RLLQ (n = 3), recurrent (n = 1), cyclic (n = 1), subacute (n = 1), worsening (n = 1), persistent (n = 1) | Not reported (n = 3)	Absent (n = 1); present (n = 2)	Preoperative continuous oral contraceptive pill (n = 1); electrocautery (n = 1); laparoscopic resection (n = 2); postoperative anti-inflammatories (n = 1). Mok-Lin et al documented endometriosis as stage 1. This was not confirmed by histopathology, as it was ablated.	Significant improvement/no pain on follow-up at >1 month (n = 2); not measured (n = 1)
Idiopathic cause (2)[36,37]	17	RLLQ (n = 2), infraumbilical (n = 1), cyclic (n = 2), radiation to back and perineum (n = 1), refractory (n = 1) | Not reported (n = 3)	Present, bilateral (n = 1); absent (n = 1)	Oral anti-inflammatory medications (n = 1)	No pain on follow-up at 1 month (n = 1)
	27			3 bedside ultrasound-guided superior hypogastric plexus blocks + injection of gonadotropin-releasing hormone agonist (n = 1)	No pain on follow-up at 3 months (n = 1)
Inguinal hernia (1)[41]	18	RLQ, dyspareunia, chronic, cyclic, dull, recurrent | Nil	Absent (n = 1)	Hernia sac dissected, right ovary and fallopian tube mobilized and returned to pelvis	Not measured
Ovarian torsion (3)[4,34,35]	9, 11, 14	RLQ (n = 1), LLQ (n = 1), RLLQ (n = 1), acute (n = 2), dull (n = 1), crampy (n = 1), worsening (n = 2), severe (n = 1), recurrent (n = 1) | Nil (n = 3)	Absent (n = 2); not reported (n = 1)	Unilateral salpingo-oophorectomy (n = 2); detorsion and fixation (n = 1)	Not measured (n = 3)

LLQ, left lower quadrant of the abdomen; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; RLQ, right lower quadrant of the abdomen; RLLQ=, right and left lower quadrants of the abdomen; RUQ, right upper quadrant of the abdomen.

* All numbers in brackets represent the number of cases.

† Uterine remnant was not removed.

‡ Acute = less than 6 months, subacute = 10 days to 3 months, chronic = 6 months or more.

Table 3
Pain Experiences after Vaginoplasty and/or Vaginal Dilation or after Removal of Obstructed Rudimentary Horn.

Study	Sample size	Age [**mean**, *range*]/ [**mean**, (SD)]/*range*	Indication | Intervention, complication(s)	Postintervention pain levels/Features of pain associated with complications	Notes on cases
Bastu et al,[2]	21	**27.8**, *13-36*	Vaginal agenesis | McIndoe vaginoplasty	Sexually active (17/21, 81%): - regular mold users who are sexually active (12/17, 71%): no dyspareunia (6/12, 50%), mild dyspareunia (5/12, 42%), moderate dyspareunia (0/12), severe dyspareunia (1/12, 8.33%) - irregular mold users who are sexually active (4/17, 24%): mild dyspareunia (1/12, 8.33%), severe dyspareunia (3/12, 25%)	Preoperative VL 0-4 cm (mean = 0.82 cm) Postoperative VL 4-11 cm (mean = 7.8 cm) Mean VL in regular vaginal mold users 6-11 cm (mean = 8.4 cm)
Cheikhelard et al, 2018 (n = 127)[43]	Surgery = 84 Dilation = 25 Intercourse = 18	Surgery = **27.1** (SD 5.2) Dilation = **23.8** (SD 4.7) Intercourse = **27.8** (SD 6.6)	Vaginal agenesis | Sigmoid colovaginoplasty (57/84, 67%), Davidov vaginoplasty (peritoneum; 8/84, 9.5%), Dupuytren vaginoplasty (epithelialization; 8/84, 9.5%), Vecchietti vaginoplasty (6/84, 7%), McIndoe vaginoplasty (5/84, 7%), dilators (25/127, 19.49%), intercourse (18/127, 14.17%)	Surgery: FSFI = 3.2 [0-6] Dilators: FSFI = 3.6 [0-6] Intercourse: FSFI = 5.4 [0-6]	Average FSFI = 3.6 [0-6]
El Saman et al,[50]	8	*20-31*	Vaginal agenesis | Laparoscopically assisted balloon vaginoplasty (8/8, 100%)	Postoperative pain scores at rest (0- 40) [0-100] Postoperative pain scores during dressing (30- 60) [0-100]	
El Sayed et al,[45]	26	**21**, *17-28*	Severe dyspareunia (18/26, 69.2%), infertility (6/26, 23.1%), primary amenorrhea (2, 7.7%) | Sigmoid colovaginoplasty (26/26, 100%): primary operation (17/26, 67%), secondary operation (9/26, 33.3%)*	Primary operation (17/26, 67%): 7/17 (41%) sexually active: superficial dyspareunia (1/7, 14.3%) Operation secondary to failed Abbe McIndoe vaginoplasty (9/26, 33.3%): sexually active (3/9, 33%): superficial dyspareunia (1/3, 33.3%).	
Gari et al,[51]	19	**21.2**, *14-38*	Difficulty in sexual intercourse and concern regarding primary amenorrhea (19, 100%) | McIndoe vaginoplasty	Sexually active (17/19, 89%): dyspareunia absent (17/17, 100%)	
Kang et al, (n = 133)[41]	Dilation = 88 Surgery = 45	Dilation = **26.4** (SD 4.40) Surgery = **26.9** (SD 4.59)	Vaginal agenesis | Dilation (88/133, 71.54%), laparoscopic Davidov vaginoplasty (45/133, 33.83%)	Post-dilation Global FSFI pain score: 10.07 (SD 3.30) Post-surgery and dilation Global FSFI pain score: 11.28 (SD 2.87) [maximum score 15]	
Borruto et al,[46]	86	*16-34*	Vaginal agenesis | Laparoscopic Vecchietti vaginoplasty	Pain/perineal discomfort requiring use of analgesia while Vecchietti traction device was in use (86/86, 100%)	Absence of dyspareunia reported at an average of 3 months in all patients
Lee et al,[48]	14	**23**, *17-40*	Vaginal agenesis | Laparoscopic neovaginoplasty using rudimentary horn serosa and pelvic peritoneum	Dyspareunia in the immediate postoperative period (2/14, 14%) Dyspareunia in later postoperative period due to upper vaginal stenosis (1/14, 7%) No postoperative dyspareunia (11/14, 79%)	All patients with dyspareunia reported no dyspareunia after vaginal dilator use
Özyazgan et al,[49]	24	**21.5** (SD 5.7)	Vaginal agenesis | Neovaginoplasty using infragluteal folds as a full-thickness skin graft donor site	Patients achieving follow-up (17/24, 71%): sexually active (8/17, 47%): no dyspareunia (8/8, 100%)	

(*continued on next page*)

Table 3 (*continued*)

Study	Sample size	Age [**mean**, *range*]/ [**mean**, (SD)]/*range*	Indication | Intervention, complication(s)	Postintervention pain levels/Features of pain associated with complications	Notes on cases
Wang et al,[47]	79 (MRKH syndrome) 83 (Control)	**24.91** (SD 5.60)	Vaginal agenesis | Laparoscopic Vecchietti vaginoplasty	Deep dyspareunia (4/79, 5.06%), vaginismus (1/79, 1.27%); MRKH syndrome FSFI pain score: 4.44 (SD 1.52), control group FSFI pain score: 4.26 (SD 0.58)	Mean VASPS = 5; reports of moderate perineal dragging pain with regular continuous traction
Zhu et al,[42]	53 (MRKH syndrome) 24 (Control)	**23.6** (SD 2.4)	Vaginal agenesis | Vaginoplasty using tissue-engineered biomaterial mesh	Sexually active patients (32/53, 76%): patients surveyed (24/32, 75%); MRKH syndrome FSFI score: 4.7 (SD 1.1), control group FSFI score: 4.3 (SD 1.5)	
Pennesi et al,[52]	615	**18**, *8-75*	Vaginal agenesis | Vaginal lengthening (331/615, 54%), no vaginal lengthening (284/615, 46%)	Dysuria with vaginal lengthening (45/331, 14%) Dysuria with no vaginal lengthening (52/284, 18.3%)	
Wang et al,[53]	1	Age at initial intervention: 21 | Age at presentation: 55	Vaginal agenesis | Sigmoid vaginoplasty, complications: introital atresia, closed neovaginal loop	Presented with pain in the RLLQ, recurrent (3 episodes), severe | Sepsis	Uterine remnant absent; underwent surgical correction of sigmoid neovagina; postintervention pain levels not measured; 2 presentations reported—no pain on second presentation
Kamath et al,[54]	1	Age at initial intervention: 18 | Age at presentation: 27	Vaginal agenesis | Sigmoid vaginoplasty, complications: perforation of sigmoid neovagina	Presented with pain in the RLLQ, not relieved by analgesics | Fever	Presence of uterine remnant not reported; underwent surgical correction of sigmoid neovagina; reported no pain at 6 months; patient denied regularly irrigating or dilating neovagina

FSFI, pain score on Global Female Sexual Function Index Questionnaire; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; RLLQ, right and left lower quadrants of the abdomen; VASPS, visual analog scale pain score; VL, vaginal length.

* Secondary to failekd Abbe-McIndoe vaginoplasty.

sexually active and had undergone the creation of a sigmoid colovaginoplasty, whereas postoperative pain scores varied in patients who underwent laparoscopically assisted balloon vaginoplasty.[45] Patients who underwent the laparoscopic Vecchietti procedure reported pain, perineal discomfort, or dragging pain requiring analgesia in the immediate postoperative days while the traction device was in use.[46,47] Studies that addressed laparoscopic neovaginoplasties with the use of newer material (rudimentary horn serosa, infragluteal folds, and tissue- engineered biomaterial mesh)[42,48,49] reported levels of postoperative dyspareunia that were low to absent and improved with subsequent vaginal dilation. Of the cases reporting complications of sigmoid colovaginoplasty (n = 2) (Table 3), the first case described introital atresia and a closed neovaginal loop, and the second reported a case of perforation of the neovagina, presenting with severe pain and persistent pain with fever, respectively. Both necessitated the surgical removal of the neovagina.[53,54]

Pain Experiences after Removal of Obstructed Rudimentary Horn

Excision of the obstructed uterine horn proved to be effective in relieving pain in the 2 studies that reported on postoperative pain experiences (Table 4). A study by Dabi et al involving 21 patients, most of whom presented with chronic cyclic pelvic pain, showed that after surgical removal of the rudimentary uterine horn in 14 patients, half reported no residual pain, whereas 21% reported the presence of residual pain.[5] Similarly, Marsh et al reported the presence of pelvic pain in 14 of 22 women with MRKH and rudimentary uterine remnants, mostly in those with a functional, secretory endometrium.[16] Among these patients, 8 underwent surgical excision of remnant tissue with no recurrence of pain after excision.

Discussion

This scoping review mapped the current literature on experiences of pain in patients with MRKH and how these are influenced by different interventions and clinical phenotypes. This review highlights the paucity of literature on pelvic and generalized persistent pain syndromes in patients with MRKH. From available evidence, it is not possible to accurately calculate prevalence of pelvic pain in women with MRKH, as most studies reporting on pelvic pain involved small cohorts of women presenting with pain from obstructed uterine horns. There were no studies that were large enough to estimate the prevalence of pelvic pain in the general population of women with MRKH. Moreover, no studies have reported on the prevalence of widespread pain or central sensitization in women with MRKH.

The review findings indicate a moderate risk of observer bias throughout the studies included, as almost all the studies assessing pain levels neglected the use of objective pain scales in acute, chronic, and postoperative pain presentations. A detailed history of pain, or examination findings, was not always clarified, although evidence in support

Table 4
Pain Experiences after Removal of Obstructed Rudimentary Horn.

Study	Sample size	**Mean age** (range)/ *Range*/ **Mean age** (SD)	Location and features of pain	Presence/absence of uterine remnant(s)	Notes on cases
Dabi et al,[5]	21	**18.9** (SD 4.8)	Chronic pelvic pain (20, 95%), cyclic pain (16, 76%)	Unilateral uterine horn remnant (1/21, 5%), bilateral uterine horn remnant (20/21, 95%)	Intervention: surgical removal of the rudimentary uterine horn (14/21, 67%), myomectomy/cystectomy/peritoneal resection (6/21, 29%) Postoperative pain levels: no residual pain (7/14, 50%), residual pain present (3/14, 21%), missing information (4/14, 29%) Intraoperative findings: ovarian cyst (2/14, 14%), uterine myoma (4/14, 29%), peritoneal endometriosis (8/14, 57.14%)
Marsh et al,[16]	48	**17.3**, *9-29*	No pelvic pain (26/48, 54%), pelvic pain (22/48, 46%), acyclic pain (8/22, 36%), cyclic pain (14/22, 64%)	In those with pelvic pain: - uterine remnant absent (8/22, 36%): nongynecologic pain (2/8, 25%), single episode (5/8), idiopathic (1/8) - uterine remnant present (14/22, 64%): with endometrium (9/14, 64%), without endometrium (5/14, 36%)	Authors attributed pain in those with a uterine remnant to the presumed presence of an obstructed remnant (9/14, 64%), unknown etiology (1/14, 7.1%), and spontaneously resolution (4/14, 29%). Pain was effectively managed with surgical removal of uteri (no pain after excision) and depot medroxyprogesterone acetate injections.

of the diagnosis of MRKH syndrome was consistently reported.

Evidence from the studies included in this scoping review indicates that in women presenting with pelvic pain with MRKH from an obstructed remnant uterus, pain is generally cyclic and mimics menstrual pain.[16,25] Of the women with acute and chronic presentations of pelvic pain, most had a functional secretory endometrium, and pelvic pain was frequently associated with concurrent endometriosis secondary to obstruction. This was supported by 2 cases of acute pelvic pain associated with endometriosis in the presence of uterine remnants and with 23 of 34 of the patients in the study by Tian et al[25] reporting experiencing pelvic pain in the context of bilateral uterine remnants and concurrent endometriosis. Most patients experienced relief of pelvic pain after excision of remnant uteri. Due consideration should be given to the fact that it is difficult to characterize cyclic pelvic pain and its relationship to the time of menses due to amenorrhea in patients with MRKH. Furthermore, there was a higher degree of selection and referral biases among these patients, wherein women without rudimentary uteri were not equally represented in studies.

It is evident that the etiology of pelvic pain in women without remnant uteri is poorly understood, particularly when it cannot be attributed to nongynecologic causes. Dysuria and dyspareunia[22,36,50] were also present in low prevalence in 1 small cohort of women; however, small sample sizes and the lack of objective pain scales being used necessitates further research into the true prevalence of these symptoms. In considering the various studies that have assessed management of pelvic pain, particularly in chronic pelvic pain postulated to be caused by secretory endometrium or endometriosis, presurgical use of combined oral contraceptive pills and gonadotropin-releasing hormone agonists can aid in stopping the decidualization of the endometrium and prevent obstructed uterine remnants.[6]

This review provides a list of differential diagnoses for patients presenting with acute, recurrent, or isolated episodes of pain. Although benign ovulatory pain can underlie cyclic pain, the possibility of ovarian torsion must always be considered with isolated presentations of severe pain. Some have postulated that lack of fixation of the adnexa and laxity of the suspensory (infundibulopelvic ligament) may also place those with MRKH at a higher risk of ovarian torsion; however, the evidence is insufficient to make a definitive conclusion.[32,34,35] The lack of fixation of ovaries to the uterus via the ovarian ligament is also seen in women with a previous hysterectomy, in whom the rate of torsion has been estimated to be 7.91 per 1000 and is frequently associated with the presence of an ovarian mass or enlarged ovary.[57,58] Among the acute presentations of pain in MRKH syndrome, 1 study included a patient who did not have rudimentary uterine remnants but presented with endometriosis lesions, although these were not histologically confirmed.[30] This could support the theory of coelomic metaplasia.[30] However, for most women with MRKH and endometriosis, this was directly associated with uterine obstruction and retrograde menstruation.

Sexual pain has also been reported and studied in women with MRKH. There are significant variations in the preference of the modality of neovagina creation depending on the clinician's capability and preference and the patient's medical history and preferences. The review highlights the varying efficacy of interventions on the basis of patients' experiences of pain, particularly in the absence of randomized control trial data among patients with MRKH. The differences in rates of dyspareunia noted with consistent and inconsistent postoperative vaginal mold use pro-

vide strong evidence for the need to continue ongoing dilation to prevent complications such as introital atresia, as well as to reduce rates of dyspareunia. Furthermore, the introduction of various interventions brought forth caveats for consideration, including the high rates of pain associated with Vecchietti traction devices postoperatively and the complications associated with colovaginoplasties. Follow-up in patients with postoperative vaginal mold use should include an awareness of the potential for atresia and prevention of complications. However, pain rates appeared lower in patients opting for surgical neovaginoplasty as opposed to dilation or sexual intercourse. This again requires further research using standardized sexual function and pain scores. This contrasts with other published studies reporting high rates of sexual satisfaction with vaginal dilation alone.[55,56] The reviewers note that there is a risk of publication bias with regard to surgical intervention studies, particularly in cases in which complications hindered the efficacy of the intervention. If these were included, a comprehensive perspective of postoperative pain levels and management could have been attained.

Further cross-sectional studies with larger sample sizes and different population demographic characteristics are needed for the evaluation of baseline pelvic and widespread pain levels and experiences in women with MRKH syndrome, using validated pelvic pain and widespread pain questionnaires, particularly given that the study conducted by Bastu et al found a high prevalence of nonspecific cyclic pain.[2] Although there is reasonably good evidence for the options for neovagina creation in patients with MRKH syndrome, further prospective studies should explore comparisons between different interventions and the levels of different types of pain experienced, with consistent pre- and postintervention usage of validated pain scales and thorough documentation of pain experiences and histories. This would not only ensure that clinicians receive evidence-based results for counseling of patients at the point of diagnosis but also elucidate the procedures or interventions that align with best practice.

Funding

This review did not receive any funding (Appendix 8).[59]

Conflicts of interest

RUG, CP, and IW have no potential conflicts to disclose. SRG is a consultant obstetrician and gynecologist and pain medicine specialist at The Royal Children's Hospital, Melbourne. ND is a consultant obstetrician and gynecologist at Cairns Hospital.

Acknowledgments

We acknowledge MRKH Australia for their ongoing support.

Appendix 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist

TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable) background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (eg, population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (eg, a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (eg, years considered, language, and publication status), and provide a rationale.	6
Information sources*	7	Describe all information sources in the search (eg, databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	27-39
Selection of sources of evidence†	9	State the process for selecting sources of evidence (ie, screening and eligibility) included in the scoping review.	6-8
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (eg, calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6-7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	7-8
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5-7
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	8, Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8-13, Tables 1-4
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	13-16, Appendix 8
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	8-13, Tables 1-4
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	8-13
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	13-16
Limitations	20	Discuss the limitations of the scoping review process.	13-16
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	13-16
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	16-17

JBI, Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and websites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (eg, quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (eg, quantitative and/or qualitative research, expert opinions, and policy documents).

From: Tricco AC, Lillie E, Zarin W, et al: PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and explanation. Ann Intern Med 2018; 169:467-473.

Appendix 2. Embase Search Terms

#1	"congenital absence of the uterus and vagina" OR "CAUV" OR "GRES" OR "Genital renal ear syndrome*" OR "MRK*" OR "Rokitansky*" OR "RKH*" OR "uterus biparitus solidus rudimentarius cum vagina solida" OR "mullerian agenes*" OR "mullerian aplasia*" OR "mullerian hypogenes*" OR "mullerian dysgenes*" OR "mullerian malformation*" OR "muellerian agenes*" OR "muellerian aplasia*" OR "muellerian hypogenes*" OR "muellerian dysgenes*" OR "vaginal agenes*" OR "vaginal aplasia*" OR "agenesis of the vagina" OR "vaginal hypogenes*" OR "vaginal dysgenes*" OR "vaginal malformation*" OR "vagina atresia*" OR "atresia vaginalis" OR "vaginal atresia" OR "MURCS association*" OR "Mullerian, renal, cervicothoracic somite*" OR "Mullerian duct aplasia, renal agenesis, and cervicothoracic somite dysplasia*" OR "Mullerian duct aplasia, unilateral renal agenesis, and cervicothoracic somite anomalies*" OR "Uterine horn*" OR "uterus horn*" OR "Rudimentary horn" OR "uterine bud" OR "uterine remnant" OR "remnant uter*" OR "unicornuate uter*"
#2	"Rokitansky syndrome"/exp OR "mullerian agenesis"/exp OR "mullerian aplasia"/exp OR "vagina aplasia"/exp OR "vagina atresia"/exp OR "uterus horn"/exp OR "unicornuate uterus"/exp
#3	#1 OR #2
#4	"pain"/exp OR "abdominal pain"/exp OR "arthralgia"/exp OR "chronic pain"/exp OR "headache"/exp OR "neck pain"/exp OR "neuralgia"/exp OR "postoperative pain"/exp OR "pain threshold"/exp OR "acute abdomen"/exp OR "abdominal angina"/exp OR "lower abdominal pain"/exp OR "backache"/exp OR "pain assessment"/exp OR "pelvis pain syndrome"/exp OR "headache and facial pain"/exp OR "colic"/exp OR "central sensitization"/exp OR "allodynia"/exp OR "dysesthesia"/exp OR "hyperalgesia"/exp OR "hyperesthesia"/exp OR "neuralgia"/exp OR "neuropathic pain"/exp OR "neuropathy"/exp OR "nociception"/exp OR "nociceptive stimulation"/exp OR "vulvodynia"/exp OR "dyspareunia"/exp OR "endometriosis"/exp OR "coccydynia"/exp OR "vaginism"/exp OR "vaginitis"/exp OR "vaginal burning sensation"/exp OR "vulvitis"/exp OR "dysmenorrhea"/exp OR "dysuria"/exp OR "cramp"/exp OR "discomfort"/exp OR "sore"/exp OR "tender"/exp OR "chronic widespread pain"/exp OR "widespread pain"/exp OR "CWP"/exp OR "myofascial pain"/exp OR "fibromyalgia"/exp OR "fibromyalgia impact questionnaire"/exp
#5	"pain*" OR "acute abdomen*" OR "abdominal angina*" OR "complex regional pain syndrome" OR "colic" OR "migraine*" OR "neuralgi*" OR "central sensitization*" OR "central sensitization" OR "nocicep*" OR "ache*" OR "allodyni*" OR "anesthesia dolorosa*" OR "causalgi*" OR "dysthesi*" OR "dysesthesi*" OR "hyperalg*" OR "hyperesthesi*" OR "hyperaesthesi*" OR "hyperpathi*" OR "neuralgi*" OR "neuropath*" OR "nocicep*" OR "vaginal burning sensation*" OR "vulvitis*" OR "adenomyos*" OR "dysmenorrhea" OR "dysmenorrhea" OR "gynaetresia" OR "dysuria" OR "dyschezia" OR "cramp" OR "discomfort" OR "sore*" OR "tender*" OR "widespread pain*" OR "CWP" OR "myofascial pain*" OR "myalgia*" OR "fibromyalgi*" OR "metralgi*" OR "hemialgi*" OR "coxalgi*" OR "inflammat*" OR "cephalgi*" OR "cephalalgi*" OR "mastalgi*" OR "diaphragmalgi*" OR "dorsalgi*" OR "enteralgi*" OR "gastralgi*" OR "hepatalgi*" OR "hysteralgi*" OR "ischialgi*" OR "lumbago" OR "mammalgi*" OR "proctalgi*" OR "rachialgi*" OR "sacralgi*" OR "tenalgi*" OR "urethralgi*" OR "copalgi*" OR "cystalgi*"
#6	#4 OR #5
#7	#3 AND #6 AND [humans]/lim

Appendix 3. MEDLINE Search Terms

#1	"congenital absence of the uterus and vagina" OR "CAUV" OR "GRES" OR "Genital renal ear syndrome*" OR "MRK*" OR "Rokitansky*" OR "RKH*" OR "uterus biparitus solidus rudimentarius cum vagina solida" OR "mullerian agenes*" OR "mullerian aplasia*" OR "mullerian hypogenes*" OR "mullerian dysgenes*" OR "muellerian agenes*" OR "muellerian aplasia*" OR "muellerian hypogenes*" OR "muellerian dysgenes*" OR "vaginal agenes*" OR "vaginal aplasia*" OR "agenesis of the vagina" OR "vaginal hypogenes*" OR "vaginal dysgenes*" OR "vaginal malformation*" OR "vagina atresia*" OR "atresia vaginalis" OR "vaginal atresia" OR "MURCS association*" OR "Mullerian, renal, cervicothoracic somite*" OR "Mullerian duct aplasia, renal agenesis, and cervicothoracic somite dysplasia*" OR "Mullerian duct aplasia, unilateral renal agenesis, and cervicothoracic somite anomalies*" OR "Uterine horn*" OR "uterus horn*" OR "Rudimentary horn" OR "uterine bud" OR "uterine remnant" OR "remnant uter*" OR "unicornuate uter*"
#2	exp pain/ OR exp "abdominal pain"/ OR exp "acute pain"/ OR exp "arthralgia"/ OR exp "back pain"/ OR exp "breakthrough pain"/ OR exp "chest pain"/ OR exp "chronic pain"/ OR exp "complex regional pain syndrome"/ OR exp "earache"/ OR exp "facial pain"/ OR exp "flank pain"/ OR exp "headache"/ OR exp "mastodynia"/OR exp "Musculoskeletal pain"/ OR exp "Myofascial pain syndrome"/ OR exp "neck pain"/ OR exp "neuralgia"/ OR exp "nociceptive pain"/OR exp "Intractable pain"/ OR exp "postoperative pain"/ OR exp "Referred pain"/ OR exp "pelvic pain"/ OR exp "pain management"/ OR exp "pain measurement"/ OR exp "pain perception"/ OR exp "pain, procedural"/ OR exp "pain, referred"/ OR exp "pain threshold"/ OR exp "pelvic pain"/ OR exp "shoulder pain"/ OR exp "visceral pain"/ OR exp "pain clinics"/ OR exp "pelvic girdle pain"/ OR exp "central nervous system sensitization"/ OR exp "nociception"/ OR exp "causalgia"/ OR exp "hyperalgesia"/ OR exp "hyperesthesia"/ OR exp "paresthesia"/ OR exp "neuritis"/ OR exp "vulvodynia"/ OR exp "dyspareunia"/ OR exp "vaginismus"/ OR exp "vaginitis"/ OR exp "gynatresia"/ OR exp "dysuria"/ OR exp "muscle cramp"/ OR exp "fibromyalgia"/
#3	"pain*" OR "acute abdomen*" OR "abdominal angina*" OR "complex regional pain syndrome" OR "colic" OR "migraine*" OR "neuralgi*" OR "central sensitization*" OR "central sensitization" OR "nocicep*" OR "ache*" OR "allodyni*" OR "anesthesia dolorosa*" OR "causalgi*" OR "dysthesi*" OR "dysesthesi*" OR "hyperalg*" OR "hyperesthesi*" OR "hyperaesthesi*" OR "hyperpathi*" OR "neuralgi*" OR "neuropath*" OR "vaginal burning sensation*" OR "vulvitis*" OR "dysmenorrhea" OR "dysmenorrhea" OR "gynaetresia" OR "dysuria" OR "dyschezia" OR "cramp" OR "discomfort" OR "sore*" OR "tender*" OR "CWP" OR "myalgia*" OR "fibromyalgi*" OR "metralgi*" OR "hemialgi*" OR "coxalgi*" OR "adenalgi*" OR "arthralgi*" OR "cardalgi*" OR "chondralgi*" OR "dactylalgi*" OR "dermatalgi*" OR "inflammat*" OR "cephalgi*" OR "cephalalgi*" OR "mastalgi*" OR "diaphragmalgi*" OR "dorsalgi*" OR "enteralgi*" OR "gastralgi*" OR "hepatalgi*" OR "hysteralgi*" OR "ischialgi*" OR "lumbago" OR "mammalgi*" OR "proctalgi*" OR "rachialgi*" OR "sacralgi*" OR "tenalgi*" OR "urethralgi*" OR "copalgi*" OR "cystalgi*"
#4	2 or 3
#5	1 and 4
#6	Limit 5 to humans

Appendix 4. CINAHL Search Terms

S1	“congenital absence of the uterus and vagina" OR "CAUV" OR "GRES" OR "Genital renal ear syndrome*" OR "MRK*" OR "Rokitansky*" OR "RKH*" OR "uterus biparitus solidus rudimentarius cum vagina solida" OR "mullerian agenes*" OR "mullerian aplasia*" OR "mullerian hypogenes*" OR "mullerian dysgenes*" OR "muellerian agenes*" OR "muellerian aplasia*" OR "muellerian hypogenes*" OR "muellerian dysgenes*" OR "vaginal agenes*" OR "vaginal aplasia*" OR "agenesis of the vagina" OR "vaginal hypogenes*" OR "vaginal dysgenes*" OR "vaginal malformation*" OR "vagina atresia*" OR "atresia vaginalis" OR "vaginal atresia" OR "MURCS association*" OR "Mullerian, renal, cervicothoracic somite*" OR "Mullerian duct aplasia, renal agenesis, and cervicothoracic somite dysplasia*" OR "Mullerian duct aplasia, unilateral renal agenesis, and cervicothoracic somite anomalies*" OR "Uterine horn*" OR "uterus horn*" OR "Rudimentary horn" OR "uterine bud" OR "uterine remnant" OR "remnant uter*" OR "unicornuate uter*"
S2	(MH "Mayer-Rokitansky-Kuster-Hauser Syndrome")
S3	S1 OR S2
S4	(MH "pain") OR (MH "abdominal pain") OR (MH "abdomen, acute") OR (MH "arthralgia") OR (MH "back pain") OR (MH "breakthrough pain") OR (MH "chest pain") OR (MH "chronic pain") OR (MH "complex regional pain syndrome") OR (MH "colic") OR (MH "earache") OR (MH "eye pain") OR (MH "facial pain") OR (MH "groin pain") OR (MH "headache") OR (MH "Musculoskeletal pain") OR (MH "muscle pain") OR (MH "Myofascial pain syndrome") OR (MH "trigger point") OR (MH "neck pain") OR (MH "neuralgia") OR (MH "piriformis syndrome") OR (MH "nociceptive pain") OR (MH "pelvic pain") OR (MH "pain postoperative") OR (MH "pain, procedural") OR (MH "pain, referred") OR (MH "shoulder pain") OR (MH "visceral pain") OR (MH "knee pain") OR (MH "treatment related pain") OR (MH "nociception") OR (MH "pain measurement") OR (MH "allodynia") OR (MH "causalgia") OR (MH "hyperalgesia") OR (MH "hyperesthesia") OR (MH "vulvodynia") OR (MH "vulvitis") OR (MH "dyspareunia") OR (MH "endometriosis") OR (MH "adenomyosis") OR (MH "dysmenorrhea") OR (MH "coccydynia") OR (MH "vaginismus") OR (MH "vaginitis") OR (MH "gynatresia") OR (MH "dysuria") OR (MH "muscle cramp") OR (MH "fibromyalgia") OR (MH "low back pain") OR (MH "tendinopathy") OR (MH "enthesopathy")
S5	"pain*" OR "acute abdomen*" OR "abdominal angina*" OR "complex regional pain syndrome" OR "colic" OR "migraine*" OR "neuralgi*" OR "central sensitization*" OR "central sensitization" OR "nocicep*" OR "ache*" OR "allodyni*" OR "anesthesia dolorosa*" OR "causalgi*" OR "dysthesi*" OR "dysesthesi*" OR "hyperalg*" OR "hyperesthesi*" OR "hyperaesthesi*" OR "hyperpathi*" OR "neuralgi*" OR "neuropath*" OR "vaginal burning sensation*" OR "vulvitis*" OR "dysmenorrhea" OR "dysmenorrhea" OR "gynaetresia" OR "dysuria" OR "dyschezia" OR "cramp" OR "discomfort" OR "sore*" OR "tender*" OR "CWP" OR "myalgia*" OR "fibromyalgi*" OR "metralgi*" OR "hemialgi*" OR "coxalgi*" OR "adenalgi*" OR "arthralgi*" OR "cardalgi*" OR "chondralgi*" OR "dactylalgi*" OR "dermatalgi*" OR "inflammat*" OR "cephalgi*" OR "cephalalgi*" OR "mastalgi*" OR "diaphragmalgi*" OR "dorsalgi*" OR "enteralgi*" OR "gastralgi*" OR "hepatalgi*" OR "hysteralgi*" OR "ischialgi*" OR "lumbago" OR "mammalgi*" OR "proctalgi*" OR "rachialgi*" OR "sacralgi*" OR "tenalgi*" OR "urethralgi*" OR "copalgi*" OR "cystalgi*"
S6	S4 OR S5
S7	S3 AND S6

Appendix 5. Cochrane Search Terms

#1	"congenital absence of the uterus and vagina" OR "CAUV" OR "GRES" OR "Genital renal ear syndrome*" OR "MRK*" OR "Rokitansky*" OR "RKH*" OR "uterus biparitus solidus rudimentarius cum vagina solida" OR "mullerian agenes*" OR "mullerian aplasia*" OR "mullerian hypogenes*" OR "mullerian dysgenes*" OR "muellerian agenes*" OR "muellerian aplasia*" OR "muellerian hypogenes*" OR "muellerian dysgenes*" OR "vaginal agenes*" OR "vaginal aplasia*" OR "agenesis of the vagina" OR "vaginal hypogenes*" OR "vaginal dysgenes*" OR "vaginal malformation*" OR "vagina atresia*" OR "atresia vaginalis" OR "vaginal atresia" OR "MURCS association*" OR "Mullerian, renal, cervicothoracic somite*" OR "Mullerian duct aplasia, renal agenesis, and cervicothoracic somite dysplasia*" OR "Mullerian duct aplasia, unilateral renal agenesis, and cervicothoracic somite anomalies*" OR "Uterine horn*" OR "uterus horn*" OR "Rudimentary horn" OR "uterine bud" OR "uterine remnant" OR "remnant uter*" OR "unicornuate uter*"
#2	[mh “pain"] OR [mh "abdominal pain"] OR [mh "acute pain"] OR [mh "arthralgia"] OR [mh "back pain"] OR [mh "breakthrough pain"] OR [mh "chest pain"] OR [mh "chronic pain"] OR [mh "complex regional pain syndrome"] OR [mh "earache"] OR [mh "facial pain"] OR [mh "flank pain"] OR [mh "headache"] OR [mh "mastodynia"] OR [mh "musculoskeletal pain"] OR [mh "myofascial pain syndrome"] OR [mh "neck pain"] OR [mh "neuralgia"] OR [mh "nociceptive pain"] OR [mh "intractable pain"] OR [mh "postoperative pain"] OR [mh "referred pain"] OR [mh "pelvic pain"] OR [mh "pain management"] OR [mh "pain measurement"] OR [mh "pain perception"] OR [mh "pain, procedural"] OR [mh "pain threshold"] OR [mh "pelvic pain"] OR [mh "shoulder pain"] OR [mh "visceral pain"] OR [mh "pain clinics"] OR [mh "pelvic girdle pain"] OR [mh "central nervous system sensitization"] OR [mh "nociception"] OR [mh "causalgia"] OR [mh "hyperalgesia"] OR [mh "hyperesthesia"] OR [mh "neuropathy"] OR [mh "vulvodynia"] OR [mh "dyspareunia"] OR [mh "vaginismus"] OR [mh "vaginitis"] OR [mh "gynatresia"] OR [mh "dysuria"] OR [mh "muscle cramp"] OR [mh "fibromyalgia"] OR [mh "myalgia"] OR [mh "arthralgia"] OR [mh "inflammation"] OR [mh "low back pain"] OR [mh "tendinopathy"] OR [mh "enthesopathy"]
#3	"pain*" OR "acute abdomen*" OR "abdominal angina*" OR "complex regional pain syndrome" OR "colic" OR "migraine*" OR "neuralgi*" OR "central sensitization*" OR "central sensitization" OR "nocicep*" OR "ache*" OR "allodyni*" OR "anesthesia dolorosa*" OR "causalgi*" OR "dysthesi*" OR "dysesthesi*" OR "hyperalg*" OR "hyperesthesi*" OR "hyperaesthesi*" OR "hyperpathi*" OR "neuralgi*" OR "neuropath*" OR "vaginal burning sensation*" OR "vulvitis*" OR "dysmenorrhea" OR "dysmenorrhea" OR "gynaetresia" OR "dysuria" OR "dyschezia" OR "cramp" OR "discomfort" OR "sore*" OR "tender*" OR "CWP" OR "myalgia*" OR "fibromyalgi*" OR "metralgi*" OR "hemialgi*" OR "coxalgi*" OR "adenalgi*" OR "arthralgi*" OR "cardalgi*" OR "chondralgi*" OR "dactylalgi*" OR "dermatalgi*" OR "inflammat*" OR "cephalgi*" OR "cephalalgi*" OR "mastalgi*" OR "diaphragmalgi*" OR "dorsalgi*" OR "enteralgi*" OR "gastralgi*" OR "hepatalgi*" OR "hysteralgi*" OR "ischialgi*" OR "lumbago" OR "mammalgi*" OR "proctalgi*" OR "rachialgi*" OR "sacralgi*" OR "tenalgi*" OR "urethralgi*" OR "copalgi*" OR "cystalgi*"
#4	#2 OR #3
#5	#1 AND #4

Appendix 6. Emcare Search Terms

#1	exp "Rokitansky syndrome"/ or exp "vagina atresia"/ or exp "vaginal agenesis"/ or exp "vagina aplasia"/ or exp "uterus horn"/ or exp "uterus malformation"/
#2	"congenital absence of the uterus and vagina" or "CAUV" or "GRES" or "Genital renal ear syndrome*" or "MRK*" or "Rokitansky*" or "RKH*" or "uterus biparitus solidus rudimentarius cum vagina solida" or "mullerian agenes*" or "mullerian aplasia*" or "mullerian hypogenes*" or "mullerian dysgenes*" or "muellerian agenes*" or "muellerian aplasia*" or "muellerian hypogenes*" or "muellerian dysgenes*" or "vaginal agenes*" or "vaginal aplasia*" or "agenesis of the vagina" or "vaginal hypogenes*" or "vaginal dysgenes*" or "vaginal malformation*" or "genital malformation*" or "vagina atresia*" or "atresia vaginalis" or "vaginal atresia" or "MURCS association*" or "Mullerian, renal, cervicothoracic somite*" or "Mullerian duct aplasia, renal agenesis, and cervicothoracic somite dysplasia*" or "Mullerian duct aplasia, unilateral renal agenesis, and cervicothoracic somite anomalies*" or "Uterine horn*" or "uterus horn*" or "Rudimentary horn" or "uterine bud" or "uterine remnant" or "remnant uter*" or "unicornuate uter*"
#3	1 or 2
#4	exp pain/ or exp "abdominal pain"/ or exp "abdominal angina"/ or exp "lower abdominal pain"/ or exp "upper abdominal pain"/ or exp "arthralgia"/ or exp "breakthrough pain"/ or exp "chronic pain"/ or exp "chronic intractable pain"/ or exp "complex regional pain syndromes"/ or exp "backache"/ or exp "epigastric pain"/ or exp "experimental pain"/ or exp "face pain"/ or exp "flank pain"/ or exp "female genital pain"/ or exp "musculoskeletal pain"/ or exp "musculoskeletal chest pain"/ or exp "myofascial pain syndromes"/ or exp "myofascial pain"/ or exp "neck pain"/ or exp "neuralgia"/ or exp "nociceptive pain"/ or exp "intractable pain"/ or exp "postoperative pain"/ or exp "post traumatic pain"/ or exp "precordial pain"/ or exp "procedural pain"/ or exp "psychogenic pain"/ or exp "pelvic pain"/ or exp "pelvis pain syndrome"/ or exp "perineal pain"/ or exp "pain, referred"/ or exp "retrosternal pain"/ or exp "shoulder pain"/ or exp "visceral pain"/ or exp "pelvic girdle pain"/ or exp "knee pain"/ or exp "leg pain"/ or exp "foot pain"/ or exp "ankle pain"/ or exp "limb pain"/ or exp "arm pain"/ or exp "hand pain"/ or exp "wrist pain"/ or exp "bone pain"/ or exp "pain assessment"/ or exp "chronic inflammatory pain"/ or exp "genital pain"/ or exp "Headache and facial pain"/ or exp "hip pain"/ or exp "inguinal pain"/ or exp "kidney pain"/ or exp "liver pain"/ or exp "non cardiac chest pain"/ or exp "pain intensity"/ or exp "spinal pain"/ or exp "stomach pain"/ or exp "urethral pain"/ or exp "urinary tract pain"/ or exp "vagina pain"/ or exp "lymph node pain"/ or exp "pain measurement"/ or exp "pain parameters"/ or exp "pain severity"/ or exp "pain threshold"/ or exp "allodynia"/ or exp "dysesthesia"/ or exp "hyperalgesia"/ or exp "hyperalgia"/ or exp "hyperesthesia"/ or exp "hyperpathia"/ or exp "paresthesia"/ or exp "neuropathic pain"/ or exp "neuropathy"/ or exp "nociception"/ or exp "vulvodynia"/ or exp "vulvitis"/ or exp "dyspareunia"/ or exp "endometriosis"/ or exp "adenomyosis"/ or exp "dysmenorrhea"/ or exp "vaginism"/ or exp "vaginitis"/ or exp "vaginal burning sensation"/ or exp "dysuria"/ or exp "cramp"/ or exp "discomfort"/ or exp "myofascial pain"/ or exp "fibromyalgia"/ or exp "fibromyalgia impact questionnaire"/ or exp "myalgia"/ or exp "otalgia"/ or exp "inflammation"/ or exp "inflammatory pain"/ or exp "low back pain"/
#5	"pain*" or "acute abdomen*" or "abdominal angina*" or "complex regional pain syndrome" or "deafferentiation" or "colic" or "trigger point" or "migraine*" or "neuralgi*" or "piriformis syndrome" or "central sensitization*" or "central sensitization" or "nocicep*" or "ache*" or "allodyni*" or "anesthesia dolorosa*" or "causalgi*" or "dysthesi*" or "dysesthesi*" or "hyperalg*" or "hyperesthesi*" or "hyperaesthesi*" or "hyperpathi*" or "paresthesi*" or "paraesthesi*" or "neuralgi*" or "neuritis" or "neuropath*" or "nocicep*" or "menstruation disturbance*" or "coccydyni*" or "vaginal burning sensation*" or "vulvitis*" or "adenomyos*" or "dysmenorrhea" or "dysmenorrhea" or "gynaetresia" or "dysuria" or "dyschezia" or "cramp" or "discomfort" or "sore*" or "tender*" or "widespread pain*" or "CWP" or "myofascial pain*" or "myalgia*" or "fibromyalgi*" or "metralgi*" or "hemialgi*" or "coxalgi*" or "otalgi*" or "adenalgi*" or "arthralgi*" or "cardalgi*" or "chondralgi*" or "dactylalgi*" or "dermatalgi*" or "inflammat*" or "cephalgi*" or "cephalalgi*" or "mastalgi*" or "diaphragmalgi*" or "dorsalgi*" or "enteralgi*" or "gastralgi*" or "hepatalgi*" or "hysteralgi*" or "ischialgi*" or "lumbago" or "mammalgi*" or "proctalgi*" or "rachialgi*" or "sacralgi*" or "tenalgi*" or "urethralgi*" or "copalgi*" or "cystalgi*"
#6	4 or 5
#7	3 and 6
#8	Limit 7 to human

Appendix 7. Scopus Search Terms

#1	TITLE-ABS-KEY("congenital absence of the uterus and vagina" OR "CAUV" OR "GRES" OR "Genital renal ear syndrome*" OR "MRK*" OR "Rokitansky*" OR "RKH*" OR "uterus biparitus solidus rudimentarius cum vagina solida" OR "mullerian agenes*" OR "mullerian aplasia*" OR "mullerian hypogenes*" OR "mullerian dysgenes*" OR "muellerian agenes*" OR "muellerian aplasia*" OR "muellerian hypogenes*" OR "muellerian dysgenes*" OR "vaginal agenes*" OR "vaginal aplasia*" OR "agenesis of the vagina" OR "vaginal hypogenes*" OR "vaginal dysgenes*" OR "vaginal malformation*" OR "vagina atresia*" OR "atresia vaginalis" OR "vaginal atresia" OR "MURCS association*" OR "Mullerian, renal, cervicothoracic somite*" OR "Mullerian duct aplasia, renal agenesis, and cervicothoracic somite dysplasia*" OR "Mullerian duct aplasia, unilateral renal agenesis, and cervicothoracic somite anomalies*" OR "Uterine horn*" OR "uterus horn*" OR "Rudimentary horn" OR "uterine bud" OR "uterine remnant" OR "remnant uter*" OR "unicornuate uter*") AND TITLE-ABS-KEY("pain*" OR "acute abdomen*" OR "abdominal angina*" OR "complex regional pain syndrome" OR "colic" OR "migraine*" OR "neuralgi*" OR "central sensitization*" OR "central sensitization" OR "nocicep*" OR "ache*" OR "allodyni*" OR "anesthesia dolorosa*" OR "causalgi*" OR "dysthesi*" OR "dysesthesi*" OR "hyperalg*" OR "hyperesthesi*" OR "hyperaesthesi*" OR "hyperpathi*" OR "neuralgi*" OR "neuropath*" OR "vaginal burning sensation*" OR "vulvitis*" OR "dysmenorrhea" OR "dysmenorrhea" OR "gynaetresia" OR "dysuria" OR "dyschezia" OR "cramp" OR "discomfort" OR "sore*" OR "tender*" OR "CWP" OR "myalgia*" OR "fibromyalgi*" OR "metralgi*" OR "hemialgi*" OR "coxalgi*" OR "adenalgi*" OR "arthralgi*" OR "cardalgi*" OR "chondralgi*" OR "dactylalgi*" OR "dermatalgi*" OR "inflammat*" OR "cephalgi*" OR "cephalalgi*" OR "mastalgi*" OR "diaphragmalgi*" OR "dorsalgi*" OR "enteralgi*" OR "gastralgi*" OR "hepatalgi*" OR "hysteralgi*" OR "ischialgi*" OR "lumbago" OR "mammalgi*" OR "proctalgi*" OR "rachialgi*" OR "sacralgi*" OR "tenalgi*" OR "urethralgi*" OR "copalgi*" OR "cystalgi*")

Appendix 8. Joanna Briggs Institute Critical Appraisal Tables

Case Reports Critical Appraisal Table

Ref #	Were the patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the postintervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Include?
1	Y	Y	N	Y	Y	N	N	Y	N
2	N	N	N	Y	Y	N	N	Y	N
3	Y	N	N	Y	Y	N	N	Y	N
4	Y	Y	N	N	N	N	N	Y	N
7	Y	Y	Y	Y	Y	Y	Y	Y	Y
13	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	Y	Y	Y	Y	Y	N	Y	Y	Y
16	Y	Y	Y	Y	Y	N	N	Y	Y
17	Y	Y	Y	Y	N	N	N	N	N
21	Y	Y	Y	Y	Y	Y	Y	Y	Y
22	Y	Y	Y	Y	Y	Y	Y	Y	Y
23	Y	Y	Y	Y	Y	Y	Y	Y	Y
25	Y	Y	Y	Y	N	N	N	Y	N
26	Y	Y	N	Y	Y	N	N	Y	N
27	Y	N	N	Y	N	N	N	Y	N
29	Y	N	N	Y	Y	N	N	Y	N
30	Y	Y	N	Y	N	Y	Y	Y	Y
31	Y	Y	Y	Y	Y	Y	Y	Y	Y
34	N	N	N	Y	Y	N	N	Y	N
35	Y	Y	Y	Y	Y	Y	Y	Y	Y
36	Y	Y	Y	Y	Y	Y	Y	Y	Y
38	Y	Y	Y	Y	N	N	N	Y	N
40	Y	Y	Y	Y	Y	N	N	N	N
41	N	N	N	Y	Y	N	N	Y	N
42	N	Y	N	Y	Y	N	N	Y	N
44	Y	Y	Y	Y	Y	N	N	Y	Y
45	Y	Y	Y	Y	Y	N	N	Y	Y
46	N	N	N	Y	Y	N	N	Y	N
56	Y	Y	Y	Y	Y	Y	Y	Y	Y
58	Y	Y	Y	Y	Y	Y	Y	N	Y
60	N	Y	N	Y	Y	N	N	Y	N
61	Y	Y	Y	Y	Y	Y	N	Y	Y
65	N	Y	N	Y	Y	N	N	N	N
66	Y	Y	Y	Y	Y	Y	Y	N	Y
68	Y	Y	Y	Y	Y	N	N	Y	Y
70	N	N	Y	Y	Y	N	N	N	N
73	Y	Y	N	Y	Y	N	N	Y	N
74	Y	Y	Y	Y	Y	Y	Y	N	Y
75	N	Y	Y	Y	Y	N	N	Y	N
80	Y	Y	N	Y	Y	N	Y	N	N
81	Y	Y	Y	Y	Y	Y	Y	Y	Y
83	N	Y	N	Y	Y	N	Y	N	N
84	Y	Y	Y	Y	Y	Y	Y	N	Y

Systematic Review Critical Appraisal Table

Ref #	Is the review question clearly and explicitly stated?	Were the inclusion criteria appropriate for the review question?	Was the search strategy appropriate?	Were the sources and resources used to search studies adequate?	Were the criteria for appraising studies appropriate?	Was critical appraisal conducted by 2 or more authors independently?	Were there methods to minimize errors in data extraction?	Were the methods used to combine studies appropriate?	Was the likelihood of publication bias assessed?	Were recommendations for policy and/or practice supported by the reported data?	Were the specific directives for new research appropriate?	Include?
53	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Cohort Studies Critical Appraisal Table

Ref #	Were the 2 groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors stated?	Were the groups/ participants free of the outcome of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was there clear reporting of clinical information of the participants?	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Was follow-up complete, and if not, were the reasons to follow up described and explored?	Were strategies to address incomplete follow-up utilized?	Was appropriate statistical analysis used?	Include?

(*continued on next page*)

(*continued*)

Case Reports Critical Appraisal Table

Ref #	Were the patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the postintervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Include?			
18	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	N
51	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
78	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y

Case Series Critical Appraisal Table

Ref #	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographic characteristics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow-up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	Include?	
5	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	
19	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	
20	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	
24	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	
39	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	
47	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	

Case-control Studies Critical Appraisal Table

Ref #	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Were the cases and controls matched appropriately?	Were the same criteria used for identification of cases and controls?	Was exposure measured in a standard, valid, and reliable way?	Was exposure measured in the same way for cases and controls?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were outcomes assessed in a standard, valid, and reliable way for cases and controls?	Was the exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?	Include?	
59	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
85	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	

Cross-sectional Studies Critical Appraisal Table

Ref #	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way>	Was appropriate statistical analysis used?	Include?
12	Y	Y	Y	Y	N	N	Y	Y	Y
14	Y	Y	Y	N	Y	Y	Y	Y	Y
36	Y	Y	Y	Y	Y	N	Y	Y	Y
64	Y	Y	Y	Y	N	N	Y	Y	Y
71	Y	Y	Y	N	Y	N	Y	Y	Y
76	Y	Y	Y	Y	N	N	Y	Y	Y
77	Y	Y	Y	Y	Y	N	Y	Y	Y
82	Y	Y	Y	N	Y	Y	N	N	N

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