PAIN

Innovative developments in pain and anxiety management for the infertile and endometriosis patient



Annelotte van Haaps

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Endometriosis, a chronic, estrogen-dependent condition, is characterized by the presence of endometrium-like tissue outside the uterus [1,2]. While the exact prevalence remains uncertain, it is estimated to affect between 2% and 10% of reproductive-aged women[1], extrapolating to 190 million women worldwide [3]. Traditionally, diagnosis relied on laparoscopy and histologic confirmation but advancements in transvaginal ultrasound and magnetic resonance imaging (MRI) have made these non-invasive methods sufficient for diagnosing endometriosis in most cases and are recommended in the current guideline [2]. The International Deep Endometriosis Analysis (IDEA) classification system is a validated method for describing endometriosis when using transvaginal ultrasound. It has been developed as a consensus on terms, definitions and measurements that can be used to describe the ultrasound characteristics of the different endometriosis phenotypes. The classification system evaluates sliding signs, soft markers (painful spots, ovarian mobility) and endometriosis presence in the anterior (bladder, urethra, vesicovaginal space) and posterior (septum rectovaginale, torus uteri, bowel, sacro-uterine ligaments) compartments. It also uses the MUSA criteria to describe adenomyosis [4]. Beside these ultrasound based classification systems, the severity and extent of endometriosis lesions are also often classified using the American Society for Reproductive Medicine (rASRM) grading system, ranging from mild (rASRM I with a limited number of lesions and few adhesions) to severe (rASRM IV with a great number of lesions, endometrioma or both, and extensive adhesions) after surgery [1]. The ENZIAN classification complements the rASRM grading system and focuses on deep endometriosis. It divides retroperitoneal structures into three compartments while also considering pelvic (e.g. bladder) and distant organ (e.g. diaphragm) involvement [5]. Furthermore, the Endometriosis Fertility Index (EFI) can be used to predict spontaneous pregnancy rate in patients with surgically documented endometriosis who attempt conception without Assisted Reproductive Therapy (ART) [6].

Endometriosis is often associated with cyclical symptoms which include dysmenorrhea, dysuria and dyschezia, but also non-cyclical symptoms which include dyspareunia, chronic pelvic pain (CPP) and infertility. Interestingly, symptom severity does not always align with disease severity, where women with mild stage endometriosis can report significant symptoms while others with severe stage endometriosis may even be asymptomatic [7]. More recently, perspectives on chronic pain have increasingly drawn of the biopsychosocial model. Rather than just explaining pain by a linear relationship between identifiable organic pathology and patient-reported symptoms, this approach conceptualizes pain and its related disability as the result of a multidimensional, dy-

1 We recognize the diverse gender identities of individuals with infertility and endometriosis. While it is important to acknowledge that not all these patients identify as women, we have chosen to utilize the term "women" for brevity and consistency, as it is commonly associated with this medical condition in existing literature.

namic interaction between physical, psychological and social factors, each affecting one another [8]. For example, severe symptoms can result in psychological diagnoses such as depression and anxiety whereas the presence of these conditions can be an important risk factor for the transition from acute to chronic pain. Therefore it is important to assess, diagnose and consequently treat chronic pain from a broad perspective where multiple social and psychosocial factors are also included, rather than just physical factors only. Endometriosis-related pain is complex and associated with several pain mechanisms that can contribute to spinal hyperalgesia [9]. This lowers the pain threshold and makes even mild stimuli, like a full bladder, painful. Additionally, fear of pain increasement can lead to protective postures, reflex pelvic floor muscle contractions and ultimately pelvic floor dysfunction which in turn can exacerbate chronic pelvic pain and dyspareunia [10]. In patients with endometriosis and CPP, it has been demonstrated that within the anterior insula of the brain, known to be important in pain processing, there is increased concentration of excitatory neurotransmitters and greater intrinsic connectivity to the same anterior insula region and medial prefrontal cortex [11]. This explains why endometriosis patients with central sensitization experience disproportional pain and negative emotions which may alter their work-related and private life. These pain mechanisms can lead to endometriosis-related pain, which in turn can detrimentally impact mental, physical and social well-being leading to reduced quality of life (QoL) and conditions like depression and anxiety [12-14]. Also, given its societal impact both through direct and indirect healthcare costs, endometriosis is comparable to other chronic conditions like Diabetes Mellitus type 2, rheumatoid arthritis and Crohn's disease [2,15,16]. This makes improving symptom management and QoL for women diagnosed with endometriosis, which this thesis focused on, crucial.

Next to improving symptom management, this thesis focused on the optimization of pain and anxiety management for the infertile patient. Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, is often associated with endometriosis and occurs in up to 50% of infertile women [2]. In general, infertility affects approximately one out of six couples in the Netherlands [17]. Besides endometriosis, tubal pathology, pelvic adhesions, ovulatory dysfunction and reduced ovarian reserve can be the cause of female infertility, while a semen factor is usually the cause of male infertility [2]. Fertility work-up is performed to find a possible explanation for the infertility and may include hysterosalpingography (HSG) to test tubal patency. During HSG, a radio-opaque medium is infused under fluoroscopy into the uterine cavity, the Fallopian tubes, and if the tubes are patent, subsequently in the abdominal cavity [18]. However, an HSG can be painful with average pain scores ranging from 3.7 to 5.0 on the Visual Analogue Score (VAS, scale 0-10cm) [19-21]. This pain and/or discomfort can result from cervical cannulation, uterine distention due to infusion of contrast, increased pressure in the Fallopian tubes and peritoneal irritation from contrast spillage [22]. Addressing this pain with local analgesics is challenging due to the complex innervation of the female reproductive

system and peritoneum [23]. In general, in the Netherlands Non-Steroid Anti Inflammatory Drugs (NSAIDs) like naproxen are advised one hour prior to HSG but this does not always provide sufficient pain relief [22,24].

When an abnormality is found during fertility work-up, or when infertility persists, procedures like Intra-Uterine Insemination (IUI) or Assisted Reproductive Therapy (ART) including In Vitro Fertilization (IVF) or Intra-Cytoplasmic Semen Injection (ICSI) may be considered. The type of treatment is dependent on the underlying pathology [25-27]. IVF/ICSI treatment can be advised in case of severe endometriosis (rASRM III-IV), a tubal factor or severe male factor e.g. oligoasthenoteratozoospermia (OAT) [17]. During ART, women undergo ovarian hyperstimulation using gonadotrophins resulting in the development of mature oocytes (follicles) which are harvested during an ultrasound-guided transvaginal oocyte retrieval [28-30]. However, since the needle passes through the vaginal wall, peritoneum and ultimately the ovarian capsule, this can cause visceral and/or insertion pain with reported mean pain scores of 6.0 (expressed using the Numeric Rating Scale (NRS), scale 0-10) [29,31,32]. Additionally, the procedure can be stressful with mean anxiety scores of 42 (measured using the State Anxiety (STAI-S), scale 20-80) immediately before retrieval [33]. During oocyte retrieval in the Netherlands, patients typically receive non-sedative pain medication (e.g. intramuscular opioids) to reduce pain, where benzodiazepines are added to reduce anxiety. Both medications are administered one hour prior to oocyte retrieval and create a state of light sedation, where pain and anxiety are reduced but patients are still responsive and able to communicate with the healthcare provider [29,34]. Nevertheless, this can be insufficient in treating all procedural pain and anxiety. In addition, non-sedative pain medication can lead to inconvenient side effects such as nausea, dizziness and tiredness [35]. Until now, apart from oocyte retrieval with general anesthesia, effective alternatives remain elusive. In addition, there is a negative association between the experienced pain, anxiety and patient satisfaction. Since high patient satisfaction is associated with better ART outcomes it is crucial that pain and anxiety management in infertility work-up and treatment is optimized [36].

Originally designed for flight simulation, military training purposes and entertainment, Virtual Reality (VR) has been found effective in alleviating treatment-associated pain and anxiety and is therefore increasingly applied in the medical field [37]. Virtual Reality places individuals in an artificial three-dimensional (3D) environment through sensory stimuli, typically visual and auditory, thereby diverting their attention from the medical procedure and its associated pain and anxiety. The VR experience is often delivered by a head-mounted display (HMD) with sensors for seamless head movement synchronization. This enhances the sense of immersion in the VR environment [38]. A systematic review with meta-analysis by Chan et al. concluded that VR is particularly effective in reducing pain during needle procedures and physiotherapy needed because of burns [39]. Furthermore, various studies have shown the effectiveness of VR in reducing pain and anxiety

during gynaecological procedures such as hysteroscopy, episiotomy repair, intra-uterine device (IUD) insertion, colposcopy and HSG [40-47]. However, not all studies on VR during gynaecological procedures agree on its pain-relieving effect. Some found no impact on pain scores or the effect was limited to anxiety scores [48-51]. One study applied VR during embryo transfer in IVF/ICSI treatment but found no difference in anxiety scores between VR and non-VR treated patients [52]. Nonetheless, VR seems a promising tool to reduce pain and anxiety, thereby hopefully improving patient satisfaction, in fertility-work up and ART.

Box 1. Research questions of this thesis

Part I
Q1. What is the effect of Virtual Reality (VR) on pain, anxiety and patient satisfaction during (outpatient) gynaecological procedures?
Q2. Does Virtual Reality (VR) contribute to pain relief during HSG ?
Q3. Does Virtual Reality (VR) contribute to pain and anxiety relief during oocyte retrieval in patients undergoing ART?

Regarding the management of endometriosis-related symptoms, there are several treatment methods available which include hormonal therapy, surgery and pain management. It is generally advised to follow the WHO step-by-step approach, e.g. the pain ladder [53]. However, this approach was originally developed for cancer patients, and might therefore not be suitable for endometriosis patients [53]. Although there are recommendations in the ESHRE guidelines on endometriosis regarding pain management, a step-by-step guideline does not exist yet [2]. At present, over-the-counter medication like paracetamol and anti-inflammatory drugs (NSAIDs) are frequently used in daily practice and although they have been proven effective in reducing dysmenorrhea in general, their efficacy on endometriosis-related pain is supported by only one limited, very low-quality evidence study [54-56]. When this step is ineffective, opioids which are part of the second and third step on the pain ladder can be prescribed. However, they might only be effective in reducing acute inflammatory pain. Due to their highly addictive character, it is recommended to prescribe them with caution and only as short-term pain management, for example the first 7 days post-operative [55]. Other medications prescribed for chronic pain, mostly by pain specialists, are anti-neuropathic medications (e.g. SSRI's, anti-depressants or anti-convulsants). They primarily modulate pain pathways of the central nervous system and have all shown promising effects on the reduction of endometriosis-related pain. However, they have not been clearly proven superior over placebo, can cause significant side effects and the number needed to treat (NNT) is high [2,57-59]. Additionally, inferior hypogastric plexus block, with local injection of an anesthetic and steroid combination, can be an effective tool to reduce chronic pelvic pain [60]. Unfortunately, all these pain-management

strategies may not be able to fully alleviate symptoms, can lead to adverse events or non-compliance of medical treatment due to unacceptable side effects [2]. Where up to 59% of women diagnosed with endometriosis still experience pain at the end of medical treatment, 11-19% of women experience no pain relief at all [61]. Therefore, alternative ways of reducing pain and improving QoL in women with endometriosis is needed.

A possible solution for reducing intractable endometriosis-related pain and improving QoL could be Spinal Cord Stimulation (SCS), an already accepted and reimbursed treatment option for neuropathic pain. The efficacy can be explained by the Gate Control Theory, which hypothesizes that electrical stimulation leads to selective closing of afferent nerve fibers and blockage of dorsal horn output, in turn diminishing pain signal transmission to the spinal cord and brain. This can lead to a reduction or even elimination of central pain perception [62,63]. Currently, SCS is still considered last-resort treatment due to its invasive nature, high costs but also potentially severe side effects such as neurological damage, infection, pleading, spinal tap and allergic reactions [64]. However, it is suggested among healthcare providers that SCS is applied sooner in the order of treatment options, especially when the positive long-term cost-effectiveness is taken into account [65]. Nonetheless, the Dutch Healthcare Institute currently only considers SCS efficacy sufficiently proven (and therefore reimbursed) for the following indications: persistent spinal pain syndrome (PSPS) type 2 with arm or leg pain, painful diabetic polyneuropathy (PDPN), complex regional pain syndrome (CRPS), other small neuropathies (SFNs) and medically refractory chronic cluster headache [65]. Although SCS is currently not reimbursed for visceral pain, whether or not related to endometriosis, there are indications that it could be effective in symptom relief and improvement of QoL [63,66-69].

Box 2. Research questions of this thesis

Part II

Q4. What would be considered standard pain management in endometriosis patients?

Q5. Could Spinal Cord Stimulation be an effective treatment for visceral pain?

Q6. What is the effect of Spinal Cord Stimulation on pain and QoL in women diagnosed with endometriosis, experiencing intractable visceral pain?

In addition to invasive treatment methods aiming to reduce endometriosis-related pain, there is growing interest in self-management strategies both among women diagnosed with endometriosis and healthcare providers. This interest is partly driven by the fact that endometriosis symptoms might be insufficiently treated with traditional treatment methods, but also because some endometriosis-related symptoms overlap with symptoms associated with Irritable Bowel Syndrome (IBS) such as bloating, abdominal cramping, back pain and fatigue and a dietary intervention is thought to positively influence both [70-72]. The self-management strategies, aiming to alleviate endometriosis-related symptoms, include dietary interventions such as a glutenfree diet, the Low FODMAP (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) diet or the so-called endometriosis diet. However, there is limited scientific evidence regarding their effectiveness on endometriosis and they are therefore currently not recommended in the European guidelines on endometriosis treatment, drafted by the European Society of Human Reproduction and Embryology (ESHRE) [2]. Nevertheless, they are frequently mentioned by patients as a method they want to apply or already applied to manage their endometriosis-related symptoms apart from the standard treatment options.

Box 3. Research questions of this thesis

Part III
Q7. What is the effect of a Low FODMAP diet and endometriosis diet on pain and quality of life in women diagnosed with endometriosis?
Q8. Based on what scientific evidence is a glutenfree diet recommended to women diagnosed with endometriosis diet?

OUTLINE OF THIS THESIS

This thesis aims to address various research questions centered around alleviating pain and anxiety in the infertile and endometriosis patient. We focus on innovative approaches like Virtual Reality (VR) and Spinal Cord Stimulation (SCS), but also frequently applied self-management strategies like dietary interventions. In Part 1 of this thesis, pain and anxiety relief for the infertile patients is targeted both during hysterosalpingography (HSG) which is part of fertility work-up and during oocyte retrieval which is part of IVF/ICSI treatment. In Chapter 2 we perform a systematic review with meta-analysis on the effectiveness of VR during (outpatient) benign gynaecological procedures. This leads to the application of VR for pain relief during HSG in Chapter 3 and for anxiety and pain relief during oocyte retrieval in IVF/ICSI treatment in Chapter 4.

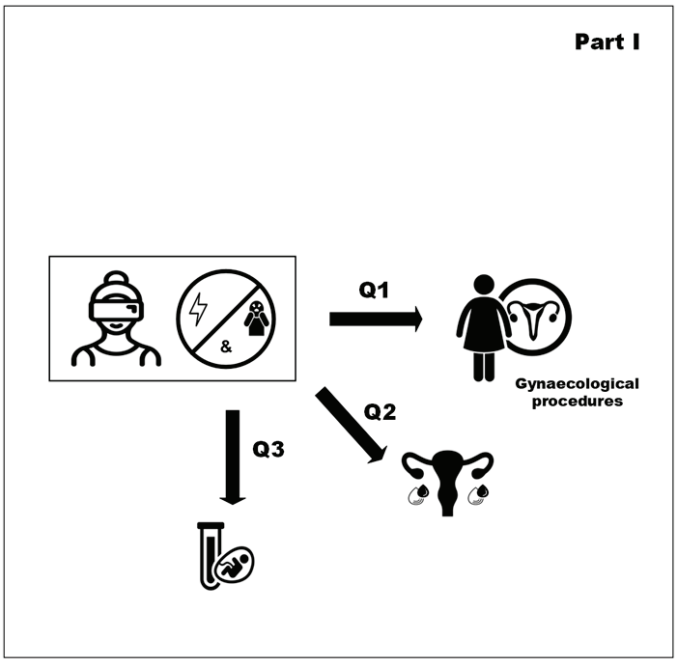

Figure 1. Graphical abstract of Part I of this thesis

In the second and third part of this thesis, our emphasis shifts to pain relief and QoL improvement in the chronic endometriosis patients. Part 2 explores the effectiveness of SCS on pain relief and QoL improvement, whereas Part 3 focuses on self-management strategies like dietary interventions. Since there is a lot of uncertainty regarding standard pain management for the chronic endometriosis patient, in Part 2 we first aim to provide national consensus on a step-by-step guideline using a focus group and modified eDelphi procedure in Chapter 5. In Chapter 6 we collect all evidence in a systematic review regarding the effectiveness of SCS on visceral pain to study whether it would be effective to apply for chronic, visceral pain. In Chapter 7 we perform a pilot study and apply SCS in nine chronic endometriosis patients, aiming to reduce their visceral pain and endometriosis-related symptoms, thereby also optimizing their QoL.

Part 3 focuses on an alternative, self-management strategy for chronic endometriosis patients which can be added to standard endometriosis management, e.g. a dietary intervention. In Chapter 8 we conduct a survey study on the experiences of endometriosis patients, regarding the endometriosis diet. Based on these findings we carry out a study in Chapter 9 comparing the effect of the Low FODMAP diet and the endometriosis diet on pain and QoL. Chapter 10 address the controversy surrounding a glutenfree diet for chronic endometriosis patients. Finally, Chapter 11 discusses our research findings and provides recommendations for future research.

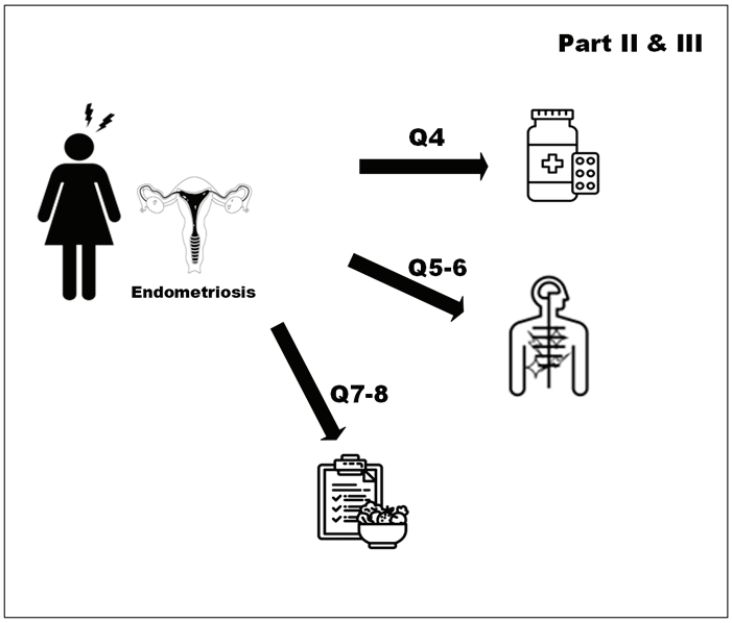

Figure 2. Graphical abstract of Part II and Part III of this thesis

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Part I

Pain and anxiety management using Virtual Reality in the infertile patient





Chapter 2

Reducing pain and anxiety with Virtual Reality in (outpatient) Gynaecological procedures: a systematic review with meta-analysis.

Annelotte van Haaps, Merel Oskam, Kim Dreyer, Kimmy Rosielle, Ralph de Vries, Ben Willem Mol, Madelon van Wely, Jan Willem Kallewaard, Anneke Schreurs, Velja Mijatovic

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ABSTRACT

Objective: Virtual Reality (VR) is increasingly used in medicine for pain and anxiety management. It has been frequently studied in the field of Gynaecology and Obstetrics and found effective during labour. However, its application during ((outpatient)) gynaecological procedures as pain and anxiety management remains underexplored. This systematic review with meta-analysis aimed to study the effect of VR on pain, anxiety and patient experiences when provided during ((outpatient)) gynaecological procedures.

Data sources: a systematic review was performed, by systematically searching PubMed, Embase, APA PsycInfo and Web of Science (Core Collection) from inception to March 20th 2024.

Study selection and synthesis: Articles on the effect of VR on pain (VAS or NRS) and anxiety (all measurement tools) during ((outpatient)) gynaecological procedures were included. Study designs had to be randomized controlled trials (RCTs) or cohort studies. Data were collected independently by two reviewers. A meta-analysis was performed to calculate mean differences (MD) with 95% Confidence Intervals (95%CI), Sensitivity analyses and a subgroup analysis were performed.

Main findings: 13 RCTs, published between 2015 and 2024, reporting on VR during ((outpatient)) gynaecological procedures for benign conditions were included. Virtual Reality significantly improved overall pain scores (MD -0.95 (95%CI -1.44 to -0.47); n=12, I^2=77%; scale 0-10), pre-procedural anxiety (MD -3.33 (95%CI -5.84 to -0.82); n=5, I^2=5%; scale 0-100) and post-procedural anxiety (MD -15.83 (95%CI -29.39 to -2.17); n=6, I^2=93%; scale 0-100).

Conclusions: the meta-analysis suggests that VR could positively influence overall pain and procedural anxiety. Not all studies reported on all outcome measures which might have introduced reporting bias and lead to an overestimation of the effect of VR. Future studies should further study the correlation between pain and anxiety and the effect of VR on this.

Relevance: this study broadens knowledge and indicates that VR could optimize pain and anxiety management in (outpatient) gynaecological procedures. It provides an alternative to pain medication, without the risks associated with pharmaceuticals, making it an attractive option.

INTRODUCTION

Originally developed for flight simulation, military training and entertainment, Virtual Reality (VR) was first used in the medical field in 1994 to simulate surgery and improve training for healthcare providers [1]. Since then, VR has also been found effective in reducing patients' pain and anxiety during medical procedures and has therefore been increasingly studied in the past decades [2, 3]. The core mechanism of VR lies in the ability to provide distraction by competing for the limited shared attentional resources with incoming nociceptive signals, thereby reducing procedural pain and anxiety [4]. This is done by placing people in an artificial three-dimensional (3D) environment, often delivered by a head-mounted display (HMD) covering the eyes, which provides a combination of visual (and auditory) stimuli to ensure optimal VR immersiveness [5]. A systematic review by Gupta et al. found that VR during medical procedures did not only provide distraction, but also enhanced the perception of control over pain, thereby increasing pain tolerance and threshold [6]. However, it is important to acknowledge that pain perception is subjective and influenced by various factors, including psychological aspects such as anxiety [7]. In the field of Gynaecology and Obstetrics, JahaniShoorab et al. (2015) was the first who successfully applied VR as pain management during episiotomy repair [8]. Thereafter, VR has been further studied and has mostly been found effective in reducing pain and/or anxiety during labour. However, evidence on the efficacy of VR during (outpatient) gynaecological procedures for benign conditions is limited [9-12].

An association has been suggested between pain and anxiety. Craven et al. found an increased demand for pain medication among emergency department patients with severe anxiety, whereas Zhang et al. found pre-operative anxiety a predictor of post-operative pain in patients undergoing laparoscopic hysterectomy [13, 14]. Moreover, a patients' psychological state can impact sedation levels, where high anxiety can impede achieving optimal sedation. Finally, anxiety is associated with adverse psychological and somatic outcomes which can negatively affect patient satisfaction [13, 15-17]. This underlines the importance of broadening pain and anxiety management [18], where Virtual Reality could offer a non-pharmacological solution. However, evidence regarding VR during ((outpatient)) gynaecological procedures is limited. Since these procedures are often associated with varying levels of anxiety and/or discomfort, VR might be beneficial. This systematic review aims to collect and study the use of VR during these procedures, evaluating its impact on anxiety, pain and patient experiences.

METHODS AND MATERIALS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [19]. The inclusion and exclusion criteria, type of studies, study selection, type of exposure, main outcomes and data were specified and prospectively registered in the PROSPERO international register of systematic reviews (CRD42022298250, registration date 4 January 2022).

Search strategy

A systematic search was conducted to identify all relevant articles regarding the effect of VR on pain and anxiety management during (outpatient) gynaecological procedures for benign conditions. We performed systematic searches in the bibliographic databases PubMed, Embase, APA PsycInfo and Web of Science (Core Collection), supported by a medical information specialist. All databases were last assessed on March 20th 2024. We additionally included a recently published study by our research team at the Amsterdam UMC, resulting in all studies from inception to June 2024 being collected. Although studies applying VR during pregnancy and/or labour were excluded, the term "Obstetrics" was added to the search to prevent an article from being missed. Article references were searched for additional relevant publications. Duplicate articles were removed. Appendix S1 shows the full search strategy.

Eligibility criteria

Randomized controlled trials (RCTs), prospective and retrospective cohort studies who applied VR with a head-mounted device (HMD) during (outpatient) gynaecological procedures and procedural pain and/or anxiety as their primary outcome were considered eligible. The field of Gynaecology was defined as the medical field specialized in health of the female reproductive system which includes its development, diagnosis, prevention and therapy of associated diagnoses [20]. Furthermore, we defined (outpatient) gynaecological procedures for benign conditions as diagnostic or therapeutic interventions which were invasive but performed with minimal to no incision, needed minimal repair or entailed excision that did not significantly alter morphology or require repair. Device placement in natural cavities, subcutaneous implants or injections were also considered gynaecological procedures [21]. Included studies involved procedures with baseline pain scores between 4.0 and 5.5 (scale 0-10) [22-26]. Studies with other primary outcomes who made mention of pain and/or anxiety management during gynaecological procedures with VR, were screened to avoid missing relevant data. We considered ultrasound a non- to minimally invasive diagnostic procedure and therefore excluded studies reporting on this. Abstract-only articles, studies not involving benign gynaecological procedures and studies on VR in pregnancy, labor or an educational setting were excluded.

Outcomes

The main outcome was pain experienced during an (outpatient) gynaecological procedure. Pain scores had to be measured on the Visual Analogue Score (VAS, scale 0.0 – 10.0 cm or 0.0 – 100.0 mm) or Numeric Rating Scale (NRS, scale 0.0 – 10.0). Although the two measuring tools are not completely interchangeable, we included both since they are considered to have a strong level of agreement and there is a significant correlation between them [27]. Procedural anxiety was chosen as secondary outcome, where all possible measurement tools that objectify anxiety were included. Other secondary outcomes focused on patient experiences including patient satisfaction, side effects and physical parameters (blood pressure, heart rate, oxygen saturation).

Selection process and data assessment

Found articles were imported into the digital program Rayyan (www.rayyan.ai), creating a database [28]. All articles were screened for inclusion by title and abstract by two independent reviewers. When an article was considered relevant, full text was obtained and screened. Only articles that fully met the inclusion criteria were included. When there was a difference in judgement, the two independent reviewers performed a consensus process where the article with its primary and secondary outcomes were discussed until consensus was reached. If necessary, a third and fourth independent researcher were consulted where the same process was performed. In case of missing data, we contacted the relevant research group, requesting completion. The Cochrane risk of bias tool was used to assess bias and quality of evidence.

Statistical analysis

When at least two studies reported one of our pre-determined outcomes, we averaged the results using random effects meta-analysis. The outcome measure reported by participants receiving VR (intervention) were compared to participants not receiving VR (control). Regarding pain, since several studies made the division between worst and overall pain scores we analyzed these separately. All pain scores were measured using NRS or VAS (scale 0-10 and 0-100). Their means and standard deviations (SD) were, where applicable, converted to a scale from 0.0 to 10.0. Medians with interquartile ranges (IQR) were transformed to a mean with SD. Anxiety scores were measured using the adjusted Amsterdam Preoperative Anxiety and Information Scale (APAIS, scale 3 – 15) [29], 10-Point Likert Scale or Numeric Rating Scale (NRS, scale 0-10) [30-32] and the State Anxiety Inventory (SAI, scale 20 – 80) [33-35]. All were converted to a scale from 0 to 100 by dividing the mean and SD of the anxiety scores by the highest number of their corresponding scale and multiply the result by 100. The same was done for patient satisfaction. In case of missing SD we used summary statistic level imputation by taking the average of the available observed variances [36].

Meta-analysis was performed using Review Manager Version 5.4. All outcomes were analyzed using the unstandardized mean difference, to calculate a mean difference (MD) with 95% Confidence Interval (95%CI) [37]. By calculating I^2, statistical heterogeneity was estimated. Sensitivity analyses were performed to assess the robustness of our findings to variations in key methodological and analytical decisions. First by calculating the standard mean difference (SMD) to correct for the different measuring tools among the studies. Second by excluding studies with high or unclear risk of bias and finally by pooling results using a fixed effects model. We performed a subgroup analysis where we differentiated between diagnostic, therapeutic and combined (diagnostic and therapeutic, e.g. biopsies) (outpatient) gynaecological procedures. Finally, quality of our findings was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment [38].

RESULTS

Study characteristics

The literature search generated a total of 14.054 references (Figure 1). After removing duplicates, 7,919 references remained. Screening led to a total of 13 studies being included [8, 26, 29-35, 39-42]. All studies were RCTs and published between 2015 and June 2024. Virtual Reality was applied during office hysteroscopy (n=5), Intra-Uterine Device (IUD) insertion (n=2), episiotomy repair postpartum (n=2), colposcopy (n=1) and hysterosalpingography (HSG) (n=3). A total of 564 patients underwent a gynaecological procedure with VR and 543 patients without VR. All included studies are presented in Table 1.

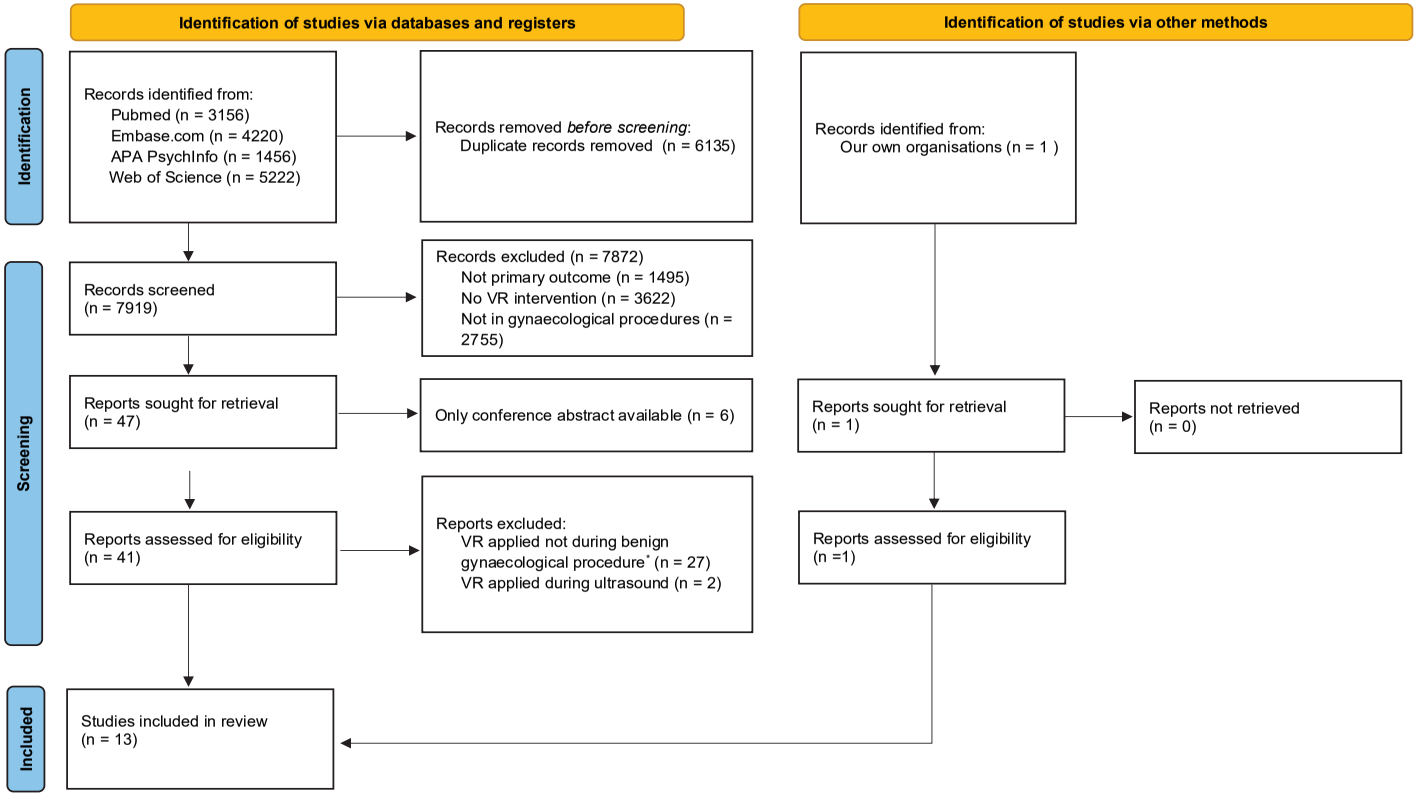


Figure 1. Flowchart of identification, screening and inclusion of articles on VR during gynaecological procedures. * Excluded because VR was applied during caesarean section (n = 3) or labour and delivery (n = 12), during obstetric procedures like amniocentesis (n = 7), to provide information or training (n = 2), during procedures associated with gynaecological cancer (n = 2) or because it entailed a study protocol (n = 1).

Table 1. Included articles and their outcome measures.

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
JahaniShoorab et al. (2015) (8)	Iran	RCT	N = 30	Episiotomy repair	5ml lidocaine hydrochloride 2% solution	*Average pain score (NRP 0-100mm) during procedure:* during skin repair 16.7 (16.5) in VR group versus 39.3 (22.5) in control group. P-value main effect P<0.0001.
Deo et al. (2020) (25)	United Kingdom	RCT	N = 40	Hysteroscopy	Self-administration of analgesics prior to the procedure (paracetamol or NSAIDs)	*Average pain score (11-Point Likert scale 0-10) during procedure:* 3.70 (2.66) in VR group versus 6.00 (2.62) in control group (P=0.009). *Worst pain score (11-Point Likert scale 0-10) during procedure:* 5.65 (2.41) in VR group versus 7.85 (2.56) in control group (P=0.008). *Anxiety (11-Point Likert scale 0-10) during procedure:* 3.30 (2.03) in VR group versus 5.45 (3.35) in control group (P=0.019).
Brunn et al. (2021) (37)	United States of America	RCT	N = 50	Hysteroscopy	Self-administration of analgesics 1 hour prior to the procedure (800mg ibuprofen)	*Worst pain score (VAS, scale 0-100mm) during procedure:* 39.70 (28.40) in VR group versus 33.40 (28.40) in control group (P=0.317). *Average heart rate (Beats Per Minute, BPM) during procedure:* 79.2 (15.5) in VR group versus 79.2 (15.6) in control group (P=0.749). *Patient satisfaction (5-Point Likert Scale):* 18/25 very satisfied; 5/25 satisfied; 2/25 neutral in VR group versus 19/25 very satisfied; 5/25 satisfied; 1/25 neutral in control group.

Table 1. Included articles and their outcome measures. (*continued*)

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
Fouks et al. (2021) (36)	Israel	RCT	N = 82	Hysteroscopy	No analgesics	*Average pain score (NRS 0-10) during procedure:* 5.0 (3.0 – 8.0) in VR group versus 5.0 (3.0 – 7.2) in control group (P=0.670). *Average respiratory rate (RR) during procedure:* 14.0 (11.0 – 16.5) in VR group versus 14.0 (13.0 – 16.0) in control group (P=0.772). *Average pulse rate (PR) during procedure:* 80.0 (73.0 – 86.0) in VR group versus 81.5 (72.8 – 90.0) in control group (P=0.704).
Bal and Kulakaç (2023) (33)	Turkey	RCT	N = 122	Hysterosalpingography (HSG)	No analgesics	*Average pain score (VAS, scale 0-10cm) during procedure:* 8.24 (1.65) in VR group versus 8.50 (1.81) in control group (p=0.240).
Benazzouz et al. (2023) (27)	France	RCT	N = 100	Intra-uterine device (IUD) insertion	Pre-medication of choice (which included paracetamol, NSAIDs, phloroglucinol, tramadol or CBD)	*Average pain score (VAS, scale 0-10cm) during procedure:* 5.1 (2.5) in VR group versus 5.4 (2.7) in control group (p=0.54). Anxiety *(VAS, scale 0-10cm) before and during (reported immediately after) the procedure:* 4.8 (2.3) in VR group versus 4.7 (2.2) in control group before the procedure (p=0.82). Score of 4.2 (2.4) in VR group versus 4.8 (2.4) in control group during the procedure (p=0.13). *Patient satisfaction (VAS, scale 0-10cm):* 9.6 (1.1) in VR group versus 9.6 (1.1) in control group (p=0.87).

Table 1. Included articles and their outcome measures. (*continued*)

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
Hecken et al. (2023) (29)	Germany	RCT	N = 247	Colposcopy	No analgesics	*Average pain score (VAS, scale 0-100mm) during procedure:* 30 (10-50) in VR group versus 20 (10-50) in control group (P=0.65). *Anxiety (STAI-S questionnaire, scale 20-80) just before and after the procedure:* 42 (37-53.5) in VR group versus 46 (36-55) in control group before the procedure (p-value not reported). Score of 32 (16.5 – 49) in VR group versus 38 (23 – 52) in control group immediately after procedure (P=0.09). *Patient satisfaction (VAS, scale 0-100mm):* 100 (95-100) in VR group versus 100 (90-100) in control group (p=0.92). *Difference in average heart rate (Beats Per Minute, BPM) between baseline and end of colposcopy: -0.5 (8.3) in VR group versus -2.5 (6.5) in control group (P=0.21).*
Orhan and Bülez (2023) (34)	Turkey	RCT	N = 50	Episiotomy repair	5ml lidocaine hydrochloride 2% solution	*Average pain score (VAS, scale 0-10cm) during procedure:* during skin repair 2.24 (2.13) in VR group versus 4.36 (1.50) in control group (p=0.001). *Patient satisfaction (VAS, scale 0-10cm):* 9.72 (0.61) in VR group versus 7.06 (1.53) in control group (p=0.001).

Table 1. Included articles and their outcome measures. (*continued*)

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
Oz and Demirci (2023) (30)	Turkey	RCT	N = 80	Intra-uterine device (IUD) insertion	Clinics standard protocol	*Average pain score (VAS, scale 0-10cm) immediately after the procedure:* 0.47 (0.55) in VR group versus 2.12 (1.27) in control group (p=0.000). *Anxiety (STAI-S questionnaire, scale 20-80) just before and after the procedure:* 68.63 before the procedure versus 23.43 after the procedure in the VR group (p<0.05). Score of 66.78 before the procedure versus 61.25 after the procedure in the control group (p<0.05). *Patient satisfaction (5-Point Likert Scale):* VR application was appropriate to reduce pain and stress: 4.85 (0.36) in VR group.
Pelazas-Hernández et al. (2023) (35)	Spain	RCT	N = 154	Hysteroscopy	No analgesics	*Average pain score (VAS, scale 0-10cm) during procedure:* 2.45 (1.17) in VR group versus 3.97 (0.52) in control group (p=0.006). *Average heart rate (Beats Per Minute, BPM) during procedure):* 76.79 (11.14) in VR group versus 72.89 (13.49) in control group (p=0.237). *Blood pressure (mmHg) during procedure:* systolic pressure 133.13 (20.76) in VR group versus 137.46 (17.09) in control group (p=0.440). Diastolic pressure 76.86 (11.14) in VR group versus 77.23 (12.29) in control group (p=0.889). *Oxygen saturation (SpO_2) during procedure:* 98.05 (1.75) in VR group versus 97.11 (2.25) in control group (p=0.732).

Table 1. Included articles and their outcome measures. (*continued*)

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
Sewell et al. (2023) (26)	United Kingdom	RCT	N = 83	Hysteroscopy	Self-administration of paracetamol and ibuprofen 1 hour prior to the procedure	*Average pain score (NRS, scale 0-10) during procedure:* 3.73 (2.39) in VR group versus 4.24 (3.07) in control group (p=0.41). *Worst pain score (NRS, scale 0-10) during procedure:* 5.32 (2.84) in VR group versus 5.07 (3.06) in control group (p=0.71). *Anxiety (NRS, scale 0-10) immediately after the procedure:* 3.29 (2.93) in VR group versus 4.79 (3.38) in control group (p=0.03). *Patient satisfaction (NRS, scale 0-10)*: 8.44 (2.27) in VR group versus 8.45 (2.27) in control group (p=0.50).

Table 1. Included articles and their outcome measures. (*continued*)

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
Sezer et al. (2023) (28)	Turkey	RCT	N = 62	Hysterosalpingography (HSG)	No analgesics	*Worst pain score (VAS, scale 0-10cm) during procedure:* 5.52 (2.40) in VR group versus 8.77 (1.84) in control group (P=0.000). *Anxiety (STAI questionnaire, scale 20-80) just before and after the procedure:* 39.42 (6.38) in VR group versus 41.93 (5.97) in control group (P=0.114) just before and 40.29 (6.49) in VR group versus 40.61 (6.29) in control group (P=0.843) immediately after the procedure. *Fear (VAS, scale 0-10cm) during procedure:* 3.71 (3.47) in VR group versus 8.26 (2.66) in control group (P=0.000). *Average pulse rate (PR) during procedure:* 90.94 (14.04) in VR group versus 84.39 (15.30) in control group (P= 0.084). *Blood pressure (mmHg) during procedure:* systolic pressure 119.06 (16.99) in VR group versus 122.32 (21.50) in control group (P=0.511). Diastolic pressure 80.71 (13.83) in VR group versus 81.06 (15.43) in control group (P=0.924). *Oxygen saturation (SpO_2) during procedure:* 97.84 (1.34) in VR group versus 97.81 (0.94) in control group (P=0.913). *Patient satisfaction (VAS, scale 0-10cm)*: 8.16 (2.43) in VR group versus 6.62 (3.36) in control group (P=0.023).

Table 1. Included articles and their outcome measures. (*continued*)

Author, year of publication	Country of origin	Type of study	Number of participants	Type of gynaecological procedure	Standard treatment	Outcome measures in mean (SD)
Rosielle et al. (2023) (24)	The Netherlands	RCT	N = 134	Hysterosalpingography (HSG)	Self-administration of analgesics 24 and 2 hours prior to the procedure (NSAIDs)	*Average pain score (VAS, scale 0-10cm) during procedure:* 5.0 (2.10) in VR group versus 4.9 (2.13) in control group (P=0.915). *Worst pain score (VAS, scale 0-10cm) during procedure:* 6.8 (2.25) in VR group versus 6.6 (2.40) in control group (P=0.574). *Anxiety (in adjusted APAIS questionnaire, scale 3-15) before procedure:* 9.2 (2.3) in VR group versus 10.1 (2.4) in control group (P=0.018). *Mean patient satisfaction (5-Point Likert Scale):* 4.1 (0.84) in VR group versus 3.8 (1.02) in control group (P=0.197).

VR technology

All studies applied VR during the entire gynaecological procedure but several different VR systems and software were used across the included studies. In three studies, the head mounted device was connected to a video player, or a smartphone was placed in the VR glasses [8, 33]. In the other studies the VR intervention consisted of VR-glasses with a built-in display. Nine studies added relaxing auditory stimuli to the VR application. No studies included manual interactivity – remote controls adding hand movements into the VR experience (Table 2).

Table 2. The VR devices used in the included studies and applications installed on the VR devices.

Study	Type of VR device used	Type of VR content used	Duration of VR intervention
Jahan-iShoorab et al. (2015) (8)	A video player (3D Blu-ray/DVD player full HD, model BD660, Indonesia) connected to a pair of video glasses (Wrap 920 system, Vuzix factory, USA).	A 3D film (IMAX Dolphin and Whales 3D 1080p). Unknown whether sound was added to the VR experience.	Not described
Deo et al. (2020) (25)	VR headset "Oculus Go" with head-mounted display with built-in audio drivers.	An 8-minute video 'Forest of Serenity' commissioned by St Giles Hospice, developed by Holosphere and narrated by Sir David Attenborough. The immersive video simulated a calming rainforest and a lake setting with animated wildlife. Sound came from the VR headset.	The video was played for the duration of the outpatient hysteroscopy and replayed when the procedure exceeded 8 minutes. Patients were allowed to stop viewing the video or remove the headset at their own discretion or in the event of side effects.
Brunn et al. (2021) (37)	VR headset "Oculus Go" by Samsung with head-mounted display with built-in audio drivers.	The Guided Meditation VR App, with multiple environments and meditations. The VR experience was standardized by choosing the Nokia Spot 1 environment and the 10-minute guided Zen meditation. Sound came from the VR headset.	Not described.
Fouks et al. (2021) (36)	VR headset was a head-mounted display (SootheVR: AppliedVR, Los Angeles, California)	An immersive module of diving in a lagoon, with background sound effects, providing relaxing auditory stimuli.	During the entire hysteroscopy procedure.
Bal and Kulakaç (2023) (33)	VR glasses; exact type of headset not described.	Scenes from nature and a feeling of comfort and peace. Unknown whether sound was added to the VR experience.	During the entire HSG procedure

Table 2. The VR devices used in the included studies and applications installed on the VR devices. (*continued*)

Study	Type of VR device used	Type of VR content used	Duration of VR intervention
Benazzouz et al. (2023) (27)	VR headset was a head-mounted PICO (Qingdao Pico Technology Co, Ltd, China)	CE-certified software from Butterfly Therapeutics (Butterfly therapeutics 'L'Effet Papillon', Laval, France), application Bliss DTx. Four virtual universes of the forest, the meadow, the ocean floor or outer space. Use of an audio headset was optional.	During the entire procedure of IUD insertion.
Hecken et al. (2023) (29)	VR headset was a head-mounted PICO G2 4K (Qingdao Pico Technology Co, Ltd, China).	CE-certified software from SyncVR (SyncVR Medical DE GmbH, Murrhardt, Germany), application SyncVR Plug and Play – Virtual Reality Studio. A video of tropical forest and underwater swimming with dolphins. Unknown whether sound was added to the VR experience.	One group prior to the procedure (not included in the meta-analysis). One group both prior and during the procedure.
Orhan and Bülez (2023) (34)	Schulzz Vrg Pro 5-7 inch smartphone 3D VR glasses	Video images with relaxing music, determined by a search method from interactive platforms and based on expert opinion. Music came from the VR glasses.	During the entire episiotomy repair.
Oz and Demirci (2023) (30)	Everest VR0022 VR Box with an android mobile phone with headset placed inside the VR box.	Video of nature walk accompanied by music coming from the VR glasses.	During the entire procedure of IUD insertion.
Pelazas-Hernández et al. (2023) (35)	VR headset "Oculus Go" by Samsung with head-mounted display with built-in audio drivers.	VR application 'A night sky'. No headphones were used, sounds came from the VR headset.	During the entire hysteroscopy procedure.
Sewell et al. (2023) (26)	VR headset was a head-mounted PICO G2.	CE-certified software from SyncVR (SyncVR Medical B.V., Utrecht, the Netherlands), application HypnoVR where 'four seasons zen environment' was played. Accompanying sound was played aloud without headphones.	During the entire hysteroscopy procedure.

Table 2. The VR devices used in the included studies and applications installed on the VR devices. (*continued*)

Study	Type of VR device used	Type of VR content used	Duration of VR intervention
Sezer et al. (2023) (28)	Virtual Reality glasses (VR SHINECON), compatible with smartphones and playing 360-degree videos. A smartphone is placed in a closed chamber on the front of the device.	A video of the sea, underwater, and forest in addition to relaxing music.	During the entire HSG procedure.
Rosielle et al. (2023) (24)	VR headset was a head-mounted PICO G2 4K device (Pico Interactive Inc., San Francisco, United States of America)	CE-certified software from SyncVR (SyncVR Medical B.V., Utrecht, the Netherlands). Containing approx. twenty relaxing movies and breathing exercises, all designed for use in medical practice. Sound was switched off.	During the entire HSG procedure.

Quality of evidence

Eight studies were considered to have a low risk for selection bias [8, 26, 29-31, 33, 34, 41]. In five studies we considered selection bias to be unknown as they randomized from a list without allocation concealment, revealed the randomization outcome at least 48 hours prior to the procedure, or did not describe their allocation process nor provided this when requested [8, 32, 35, 39, 40]. Since none of the studies were blinded, risk of performance- and detection bias was considered high [8, 26, 29-35, 39-42]. Brunn et al. [42] and Deo et al. [30] mentioned the presence of recall bias but provided no further details. Therefore we assessed their "other bias" as unknown (Figure 2). When assessing the included studies on trustworthiness according to the Trustworthiness in RAndomised Controlled Trials (TRACT) checklist, no major concerns were found apart from the fact that some studies were retrospectively registered [43]. No studies were therefore excluded (Appendix S2).

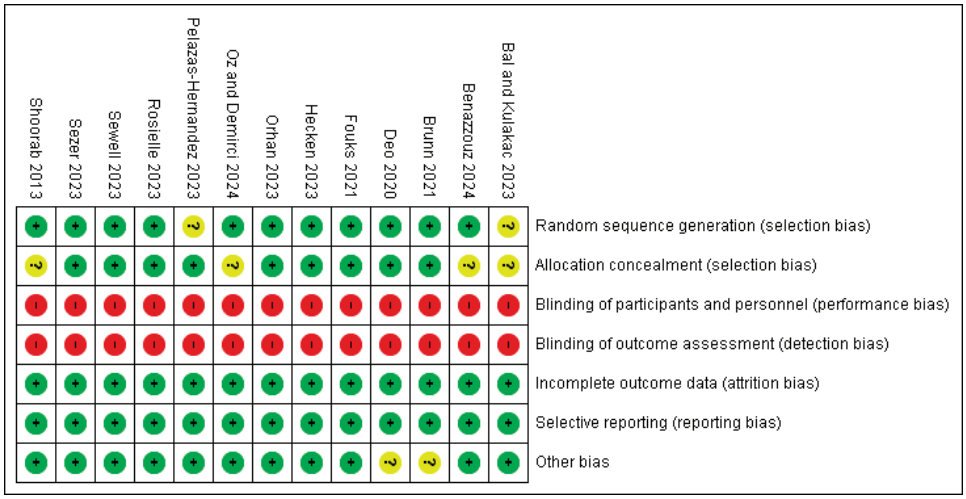


Figure 2. Risk of bias for all included studies.

When assessing certainty of evidence according to the GRADE assessment, we considered it possible that the inability to blind participants and study personnel affected pain and/or anxiety. Due to high heterogeneity of data in all but pre-procedural anxiety and the use of different measurement tools for pain and anxiety, we considered the level of inconsistency *serious* in overall pain, worst pain, pre- and post-procedural anxiety. Since risk of other bias and imprecision were considered *not serious*, this led to certainty of evidence being moderate. In patient satisfaction and heart rate, certainty of data were considered high (Table 3).

Table 3. Evidence assessment on the different outcomes, according to the GRADE approach. Acquired using Review Manager 5.4 software.

Participants (studies) Follow-up	Risk of bias	Inconsis-tency	Indirectness	Imprecision	Overall certainty of evidence	Mean Difference (95%CI) with Virtual Reality
Average pain during outpatient benign gynaecological procedures						
1045 (12 RCTs)	not serious	serious[a,b,c]	not serious	not serious	⊕⊕⊕◯ Moderate[a,b]	MD **0.95 lower** (1.44 lower to 0.47 lower)
Worst pain during outpatient benign gynaecological procedures						
370 (5 RCTs)	not serious	serious[a,b,c]	not serious	not serious	⊕⊕⊕◯ Moderate[a,b]	MD **0.87 lower** (2.33 lower to 0.59 higher)
Pre-procedural anxiety during outpatient benign gynaecological procedures						
537 (5 RCTs)	not serious	serious[d,e]	not serious	not serious	⊕⊕⊕◯ Moderate[d,e]	MD **3.33 lower** (5.84 lower to 0.82 lower)
Post-procedural anxiety during outpatient benign gynaecological procedures						
525 (4 RCTs)	not serious	serious[c,d,e]	not serious	not serious	⊕⊕⊕◯ Moderate[c,d,e]	MD **15.83 lower** (29.49 lower to 2.17 lower)
Patient satisfaction during outpatient benign gynaecological procedures						
590 (6 RCTs)	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ High	MD **0.82 higher** (0.2 lower to 1.84 higher)
Heart Rate during outpatient benign gynaecological procedures						
513 (5 RCTs)	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ High	MD **2.1 higher** (0.31 higher to 3.9 higher)

[a] Some studies reported only on worst pain scores, where others reported only on average pain scores. Finally, some studies reported on both.

[b] Some studies found significant differences in pain scores, where others did not.

[c] High heterogeneity of data.

[d] Not all studies reported on anxiety scores.

[e] Some studies reported only on pre-procedural anxiety, where other reported only on post-procedural anxiety scores. Finally, some studies reported on both.

Patient experiences during (outpatient) gynaecological procedures

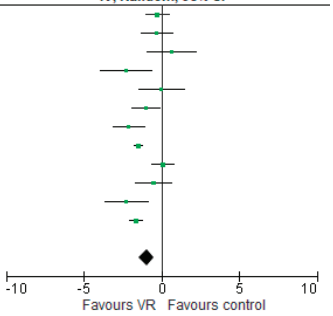
Overall and worst pain

All studies reported on procedural pain, either with overall pain scores [8, 26, 32, 34, 35, 39-41], worst pain scores [33] or both [29-31, 42]. A significant mean difference (MD) of -0.95 ((95%CI -1.44 to -0.47); n=12, I^2=77%) in overall pain and a non-significant mean difference of -0.87 ((95%CI -2.33 to 0.59); n=5, I^2=91%) in worst pain were seen in favour of VR. Both were measured on a scale from 0 to 10 (Figure 3). Expressed as standardized mean difference (SMD) these were -0.56 ((95% CI -0.94 to -0.18); I^2=88%) for overall pain and -0.35 ((95% CI -0.98 to 0.28); I^2=88%) for worst pain (Appendix Figure 1).

A. Overall pain experienced during benign outpatient gynaecological procedures

Study or Subgroup	Virtual reality Mean	SD	Total	Standard care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bal and Kulakaç 2023	8.24	1.65	42	8.5	1.81	40	9.9%	-0.26 [-1.01, 0.49]
Benazzouz 2024	5.1	2.5	47	5.4	2.7	48	8.1%	-0.30 [-1.35, 0.75]
Brunn 2021	3.97	2.84	25	3.34	2.84	25	5.5%	0.63 [-0.94, 2.20]
Deo 2020	3.7	2.66	20	6	2.62	20	5.2%	-2.30 [-3.94, -0.66]
Fouks 2021	5	3.7	44	5	3.11	38	5.9%	0.00 [-1.47, 1.47]
Hecken 2023	2	2.96	82	3	2.96	83	9.0%	-1.00 [-1.90, -0.10]
Orhan 2023	2.24	2.13	25	4.36	1.5	24	8.2%	-2.12 [-3.15, -1.09]
Pelazas-Hernández 2023	2.45	1.17	82	3.97	0.52	72	12.5%	-1.52 [-1.80, -1.24]
Rosielle 2023	5	2.1	70	4.9	2.13	65	10.2%	0.10 [-0.61, 0.81]
Sewell 2023	3.73	2.39	41	4.24	3.07	42	7.3%	-0.51 [-1.69, 0.67]
Shoorab 2013	1.67	1.65	15	3.93	2.25	15	6.2%	-2.26 [-3.67, -0.85]
Öz and Demirci 2024	0.47	0.55	40	2.12	1.27	40	11.9%	-1.65 [-2.08, -1.22]
Total (95% CI)			**533**			**512**	**100.0%**	**-0.95 [-1.44, -0.47]**

Heterogeneity: Tau² = 0.47; Chi² = 46.81, df = 11 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.86 (P = 0.0001)



B. Worst pain experienced during benign outpatient gynaecological procedures

Study or Subgroup	Virtual reality Mean	SD	Total	Standard care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Brunn 2021	3.5	1.56	25	3	0.95	25	21.4%	0.50 [-0.22, 1.22]
Deo 2020	5.56	2.41	20	7.85	2.56	20	18.0%	-2.29 [-3.83, -0.75]
Rosielle 2023	6.8	2.25	70	6.6	2.4	65	21.2%	0.20 [-0.59, 0.99]
Sewell 2023	5.32	2.84	41	5.07	3.06	42	19.3%	0.25 [-1.02, 1.52]
Sezer 2023	5.52	2.4	31	8.77	1.84	31	20.1%	-3.25 [-4.31, -2.19]
Total (95% CI)			**187**			**183**	**100.0%**	**-0.87 [-2.33, 0.59]**

Heterogeneity: Tau² = 2.46; Chi² = 42.60, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.17 (P = 0.24)

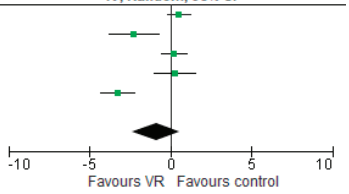


Figure 3. Reported overall and worst pain scores in the different studies of women undergoing either office hysteroscopy, Intra-Uterine Device (IUD) insertion, episiotomy repair, colposcopy and hysterosalpingography (HSG). Scores were measured in VAS (scale 0-10cm or 0-100mm) or NRS (scale 0-10) and converted to a scale from 0-10. Forest plot of meta-analysis reporting on reported pain scores. (A) Overall pain score. (B) Worst pain score. Mean difference and 95% CI. MD<1 favour VR intervention, MD>1 favour control group.

Pooling only data of studies with low risk of selection bias, the MD of overall pain scores was almost unchanged but lost significance (MD -0.74 (95%CI -1.52 to 0.04); n=8, I^2=70%). When removing retrospectively registered studies, we saw no change in overall (MD -0.88 (95%CI -1.60 to -0.17); n=6, I^2=79%) and worst pain (MD -0.93 (95% CI -3.19 to 1.33); n=3, I^2=93%). Funnel plot analysis suggested a consistent negative effect across the studies but no publication bias or small-study effects (Appendix Figure 2). Due to high heterogeneity

of data we performed sensitivity analyses, where worst pain scores became significant when using the fixed-effects model (Table 4).

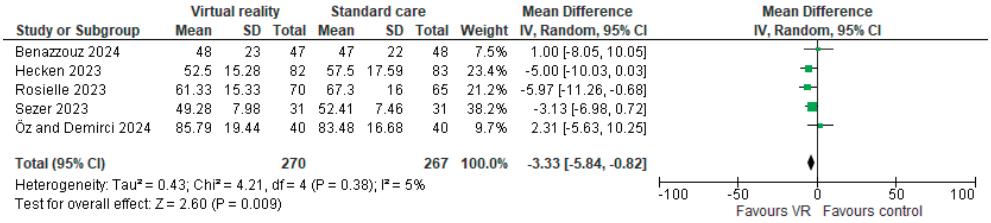
Table 4. Sensitivity analysis using the fixed-effects model and the random-effects model. When negative numbers are displayed, the mean differences are in favour of VR.

Outcome measure	Random effects MD (95%CI)	Fixed effects MD (95%CI)
Average pain scores	-0.95 (-1.44, -0.47)	-1.25 (-1.44, -1.06)
Worst pain scores	-0.87 (-2.33, 0.59)	-0.43 (-0.86, -0.01)
Pre-procedural anxiety	-3.33 (-5.84, -0.82)	-3.36 (-5.77, -0.94)
Post-procedural anxiety	-15.83 (-29.49, -2.17)	-7.41 (-10.44, -4.37)
Patient satisfaction	0.82 (-0.20, 1.84)	0.73 (0.44, 1.02)
Heart rate	2.10 (0.31, 3.90)	2.10 (0.31, 3.89)

Procedural anxiety

Seven studies evaluated procedural anxiety. Since it was measured either pre-procedural [29], post-procedural [30, 31] or both [32-35], these were analyzed separately (scale 0-100). Pre-procedural anxiety (MD -3.33 (95%CI -5.84 to -0.82); n=4, I^2=5%) and post-procedural anxiety (MD -15.83 (95%CI -29.49 to -2.17); n=5, I^2=93%) showed a significant favourable effect of VR (Figure 4). Expressed as standardized mean difference (SMD) these were -0.20 ((95%CI -0.40 to 0.01); I^2=29%) for pre-procedural anxiety and -0.61 ((95%CI -1.10 to -0.12); I^2=86%) for post-procedural anxiety (Appendix Figure 3).

A. Pre-procedural anxiety measured during benign outpatient gynaecological procedures



B. Post-procedural anxiety measured during benign outpatient gynaecological procedures

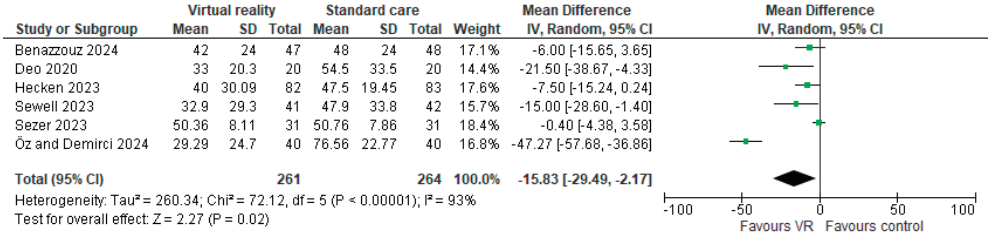


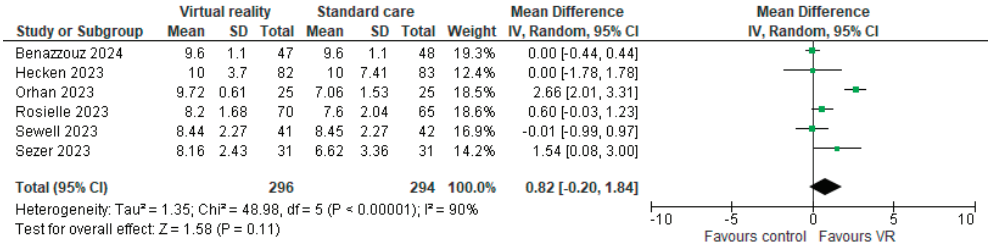
Figure 4. Reported anxiety scores in the different studies of women undergoing either office hysteroscopy, Intra-Uterine Device (IUD) insertion, colposcopy and hysterosalpingography (HSG). Scores were measured in STAI, APAIS, NRS or 10-point Likert scale and converted to a scale from 0-100. Forest plot of meta-analysis reporting on reported anxiety scores. (A) Pre-procedural anxiety. (B) Post-procedural anxiety. Mean difference and 95% CI. MD<1 favour VR intervention, MD>1 favour control group.

After removing studies with an unknown risk of selection bias, the MD in pre-procedural anxiety was unchanged (MD -4.36 (95%CI -7.00 to -1.71), n=3, I^2=0%). In post-procedural anxiety, the MD decreased but remained significant (MD -8.50 (95%CI -16.97 to -0.04), n=4, I^2=71%). When removing retrospectively registered studies, the MD became non-significant in post-procedural anxiety (MD-5.32 (95%CI -11.05 to 0.41); n=4, I^2=52%). We performed a sensitivity analysis for post-procedural anxiety because of high heterogeneity of data, by analyzing data according to the fixed effects model (Table 4).

Patient satisfaction

In total, nine studies reported on patient satisfaction. Six studies reported on patient satisfaction using VAS, NRS or a 5-Point Likert Scale. No significant difference was seen in patient satisfaction, between intervention and control (MD 0.82 (95%CI -0.20 to 1.84); n=6, I^2=90%. Scale 0-10) (Figure 5A). Three studies used interviews to objectify patient satisfaction (Table 5).

A. Patient satisfaction



B. Heart rate (HR; in BPM) measured during the procedures

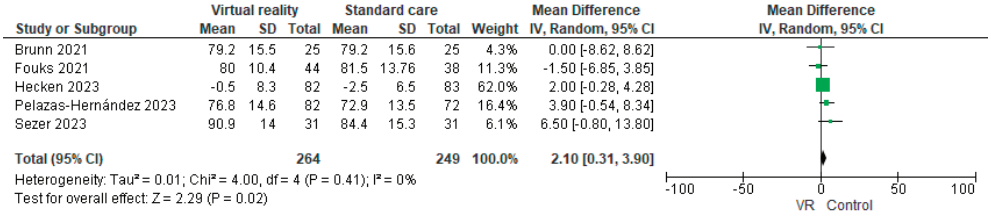


Figure 5. Reported patient satisfaction in NRS (scale 0 – 10) and heart rate measured during the procedures. Patient satisfaction was measured in the different studies of women undergoing either office hysteroscopy, Intra-Uterine Device (IUD) insertion, episiotomy repair, colposcopy and hysterosalpingography (HSG). Heart rate (HR) was measured in studies with women undergoing either HSG or hysteroscopy measured in the different studies Forest plot of meta-analysis reporting on reported patient satisfaction. Mean difference and 95% CI. MD<1 favour control group, MD>1 favour VR intervention.

Table 5. Patient satisfaction reported during office hysteroscopy, during Intra-Uterine Device (IUD) insertion, during episiotomy repair, during colposcopy and during hysterosalpingography (HSG). If possible, P-values were reported.

Author, year of publication	Gynaecological procedure	Patient satisfaction	P-value
Deo et al. (2020) (25)	Hysteroscopy	**Semi-structured interviews. Positive experiences:** - Relaxation that distracted from pain - VR blocked sight of doctors and equipment - Pain not completely removed but distraction element aided in pain reduction and immediate recovery after instance of sharp pain - VR headset was comfortable **Negative experiences:** - No effect of VR technology - VR only effected during low to moderate pain - VR headset was not comfortable and claustrophobic (1/40 participants) - VR caused non-severe nausea (1/40 participants)	Not applicable
Brunn et al. (2021) (37)	Hysteroscopy	**Very satisfied**: 18/25 in VR group vs. 19/25 in control group. **Satisfied**: 5/25 in VR group vs. 5/25 in control group. **Neutral**: 2/25 in VR group vs. 1/25 in control group. **Unsatisfied**: 0/25 in VR group vs. 0/25 in control group. **Very unsatisfied**: 0/25 in VR group vs. 0/25 in control group. 88% found music very or slightly calming. 84% found medication very or slightly calming. 72% found VR environment very or slightly realistic.	Overall p-value: 1.000
Benazzouz et al. (2023) (27)	Intra-uterine device (IUD) insertion	Patient satisfaction (VAS, scale 0-10cm): 9.6 (1.1) in VR group versus 9.6 (1.1) in control group.	P=0.87
Hecken et al. (2023) (29)	Colposcopy	Patient satisfaction (VAS, scale 0-100mm): 100 (95-100) in VR group versus 100 (90-100) in control group.	P=0.92
Orhan and Bülez (2023) (34)	Episiotomy repair	Patient satisfaction (VAS, scale 0-10cm): 9.72 (0.61) in VR group versus 7.06 (1.53) in control group.	P=0.001
Öz and Demirci (2023) (30)	Intra-uterine device (IUD) insertion	- Watching a video with VR was effective and helpful in reducing stress (5-Point Likert scale): 4.83 (0.39) in VR group. - Watching a video with VR helped to focus attention elsewhere (5-Point Likert scale): 4.88 (0.34) in VR group. - I liked and was satisfied with the method of watching videos with the VR application: 4.88 (0.34) in VR group. - The video and music I watched with VR was motivating and helped me feel less pain: 4.83 (0.39) in VR group. - VR application was appropriate to reduce pain and stress: 4.85 (0.36) in VR group.	Not applicable.
Sewell et al. (2023) (26)	Hysteroscopy	Patient satisfaction (NRS, scale 0-10): 8.44 (2.27) in VR group versus 8.45 (2.27) in control group.	P=0.50

Table 5. Patient satisfaction reported during office hysteroscopy, during Intra-Uterine Device (IUD) insertion, during episiotomy repair, during colposcopy and during hysterosalpingography (HSG). If possible, P-values were reported. (*continued*)

Author, year of publication	Gynaecological procedure	Patient satisfaction	P-value
Sezer et al. (2023) (28)	Hysterosalpingography (HSG)	- Patient satisfaction (VAS 0-10cm) 15 minutes after HSG: 8.16 (SD 2.43) in VR group vs. 6.62 (3.36) in control group. - 87.1% of women wanted to use VR technology again if they had to undergo another HSG. 96.8% would recommend VR technology to other women undergoing an HSG.	P = 0.023 Not applicable
Rosielle et al. (2024) (24)	Hysterosalpingography (HSG)	- Patient satisfaction (5-Point Likert scale): 4.12 (0.86) in VR group vs. 3.78 (0.90) in control group. - Another HSG with VR (5-Point Likert scale): 3.43 (1.35) in VR group vs. 3.61 (1.37) in control group. - Another HSG without VR (5-Point Likert scale): 2.73 (1.25) in VR group vs. 3.63 (1.38) in control group. - Recommend VR technology to other women undergoing an HSG (5-Point Likert scale): 4.23 (0.91) in VR group. Not measured in the control group.	0.197 0.608 0.005 Not applicable

Side effects

Side effects included nausea and/or vomiting, blurred vision and dizziness. [29-31, 40-42]. They were short-lasting without serious consequences (Table 6). A meta-analysis could not be performed but the two studies comparing intervention to control found no statistical difference in side effects [29, 41].

Table 6. included studies and their reported side effects

Author, year of publication	Side effects Virtual Reality	Side effects control group	P-value
JahaniShoorab et al. (2015) (8)	Not described	Not described	Not applicable
Deo et al. (2020) (25)	1/20 nausea during the procedure 1/20 pre-existing claustrophobia resulting in removal of VR intervention	No side effects No side effects	Not applicable Not applicable
Brunn et al. (2021) (37)	1/25 blurred vision during procedure, transient after removal of VR glasses	No side effects	Not applicable
Fouks et al. (2021) (36)	7/44 nausea or vomiting during the procedure 10/44 dizziness during the procedure	6/38 nausea or vomiting during the procedure 9/38 dizziness during the procedure	P=0.866 P=0.685
Bal and Kulakaç (2023) (33)	Not described	Not described	Not applicable
Benazzouz et al. (2023) (27)	Not described	Not described	Not applicable
Hecken et al. (2023) (29)	Not described	Not described	Not applicable
Orhan and Bülez (2023) (34)	Not described	Not described	Not applicable
Oz and Demirci (2023) (30)	Not described	Not described	Not applicable
Pelazas-Hernández et al. (2023) (35)	1/82 dizziness during the procedure	3/72 dizziness during the procedure	Not applicable
Sewell et al. (2023) (26)	2/41 mild nausea not requiring anti-emetics	1/42 mild nausea not requiring anti-emetics 1/42 pre-syncope 1/42 brief loss of consciousness from presumed vasovagal episode	
Sezer et al. (2023) (28)	Not described	Not described	Not applicable
Rosielle et al. (2023) (24)	Nausea average score of 1.6 (SD 1.08) * Dizziness average scores of 1.6 (SD 0.98) * Headache average score of 1.1 (SD 0.57) * Blurred vision average score of 1.3 (SD 0.84) *	Nausea average score of 1.7 (SD 1.18) * Dizziness average scores of 1.7 (SD 1.08) * Headache average score of 1.2 (SD 0.48) * Blurred vision average score of 1.2 (SD 0.41) *	P=0.422 P=0.583 P=0.482 P=0.489

* Measured using the 5-Point Likert scale ranging from "1" representing none of the time to "5" representing all the time.

Physical parameters

A meta-analysis could only be performed on the physical parameter of heart rate. A significant higher heart rate was seen in the control group (MD 2.10 (95%CI 0.31 to 3.90); n=5, I^2=0%) (Figure 5B).

Subgroup analyses

Only a subgroup analysis could be performed where studies reporting on the use of VR during diagnostic procedures [29, 33, 39] were analyzed separately from studies during therapeutic procedures [8, 26, 32, 35] and studies during procedures where diagnostics were combined with small procedures like biopsies [30, 31, 34, 40-42]. Significant differences favoring VR were seen in overall pain for therapeutic and combined gynaecological procedures, in pre-procedural anxiety for diagnostic gynaecological procedures and in post-procedural anxiety for combined gynaecological procedures (Appendix Figure 4).

DISCUSSION

To the best of our knowledge, this is the first systematic review with meta-analysis evaluating the effect of VR on pain and anxiety during (outpatient) gynaecological procedures for benign conditions. Our results suggest that VR could be contributory in reducing overall pain and anxiety, with subgroup analyses suggesting VR might be an effective tool to reduce overall pain in therapeutic and combined gynaecological procedures, pre-procedural anxiety in diagnostic procedures and post-procedural anxiety in combined gynaecological procedures. Analysis with the fixed-effects model confirmed large variability across the included studies, confirming that an analysis with random-effects model was most appropriate. Based on the GRADE assessment, certainty of evidence was considered moderate.

Strengths and limitations

Our review has several strengths. We established a clear research question and protocol, which was prospectively registered in PROSPERO. The review adhered to PRISMA guidelines. Data extraction and validation were done independently and blinded using Rayyan. Any discrepancies during article screening were meticulously addressed and if necessary a third or fourth independent researcher was consulted to reach consensus. In case of missing data or study design details, the relevant research group was contacted with the request of completing these. Trustworthiness of the included studies was assessed using the TRACT checklist. Finally, a subgroup- and sensitivity analysis were performed to ensure proper statistical analysis. Despite these strengths, our review also has several limitations. Not all studies reported on all outcome measures which might have introduced reporting bias with an overestimation of the effect of VR on the outcome measures. Publication bias might have contributed to this overestimation because articles with positive

effects on an intervention are more likely to be published. Although studies without an effect of VR on pain and/or anxiety were included, this bias should be taken into account when interpreting the results. Furthermore, a considerable level of heterogeneity was seen in reported pain and post-procedural anxiety with potential influential factors such as participant characteristics, blinding, study quality, different measurement tools and different gynaecological procedures where VR was applied. JahaniShoorab et al. reported a significant discrepancy in episiotomy depth between the VR and non-VR group, potentially contributing to data heterogeneity [8]. The fact that only five out of thirteen studies had no analgesics added to the VR intervention, might have further contributed to data heterogeneity. Also because Orhan and Bülez and JahaniShoorab et al., who provided Virtual Reality during episiotomy repair, did not make mention of labour analgesics such as an epidural. All included studies were randomized controlled trials, which might be explained by the fact that VR in medical procedures is a relatively new development and has not been widely studied. It is still to be determined in which medical area and on what procedure-associated factor it is most effective. The inability to use blinding due to the nature of the intervention may have introduced performance and detection bias. The Hawthorne effect might have been influential, where the knowledge of receiving an intervention affects pain- and/or anxiety scores[44].

Interpretation

Our meta-analysis showed a small but significant improvement in overall pain scores. It is debatable whether this difference is clinically relevant as Cepeda et al. considered a decrease of at least 1.3 in NRS units (20%) as relevant minimal pain reduction in moderate acute procedural pain [45]. Since our findings fall below this threshold, VR may not provide clinically relevant pain reduction. This could be explained by suboptimal VR immersiveness, which is highlighted by previous studies as key to effective pain management [5, 46-52]. Furthermore, in a clinical setting VR is generally considered most effective for mild pain, where the distraction mechanism is not overridden by pain signals. In our subgroup analysis however, VR seemed to achieve clinically relevant pain reduction during therapeutic procedures, which are associated with higher pain levels compared to diagnostic procedures. The included studies did not provide a clear explanation for this finding, except the fact that administration of pain medication varied in studies providing VR during diagnostic procedures whereas all studies providing VR during therapeutic procedures applied pain medication. Furthermore, greater uncertainty associated with diagnostic and combined procedures might have affected experienced pain. Patients may feel they have more control during therapeutic procedures, as these are aimed at treating their condition. Diagnostic procedures are often associated with more uncertainty regarding the results and a potential diagnosis which can contribute to a greater sense of helplessness and lack of control, leading to increased procedural anxiety and ultimately procedural pain [53]. We found that VR significantly reduced procedural anxiety, with the subgroup analysis finding it most effective when there was a diagnostic element.

By providing distraction using VR, attention can be shifted from the medical procedure to pleasant or interesting stimuli, thereby reducing negative emotions such as anxiety [54-56]. Furthermore, optimizing anxiety management with VR might also improve pain management, thereby transcending the clinical relevant threshold of 1.3 units. This is supported by the findings by Craven et al. and Zhang et al. where significant associations between pain and anxiety were seen [13, 14].

We found no significant difference in patient satisfaction. It could be that relief over completion of the procedures resulted in no discernible difference in satisfaction scores between intervention and control. However, to our knowledge there are no studies supporting this and two of the included studies contradict this since they found significant better satisfaction scores when VR was applied [26, 33]. Patient satisfaction is crucial as it can strongly influence therapy compliance, reduce healthcare utilization, minimize malpractice litigation and contribute to a better prognosis [57]. Healthcare providers increasingly recognise the importance of evaluating treatment innovations from a holistic approach which also considers improvements in other measures such as quality of life, medication use or patient satisfaction rather than solely symptom reduction [58]. This approach considers the complexity of pain and its impact and evaluates improvements across a range of health domains that patients consider relevant by establishing minimal clinical important differences (MCIDs). Creating composite scores, where at least two outcome measures are combined into one single measure, can aid in evaluating the broader impact of health interventions [58, 59]. We recommend future studies to evaluate interventions from a holistic approach, ensuring that treatment efficacy is studied from all aspects.

CONCLUSION

This systematic review with meta-analysis found a significant reduction in overall pain and procedural anxiety in favour of VR. Subgroup analysis suggests that VR might be more effective for overall pain during therapeutic procedures, and for procedural anxiety during procedures with a diagnostic element. The results should be interpreted cautiously due to data heterogeneity and potential bias. Future studies should explore the strong correlation between anxiety and perceived pain and apply a more holistic approach where the effect on composite health domains is considered much more important.

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Chapter 3

No pain relief by Virtual Reality during hysterosalpingography (HSG): results from a randomized controlled trial

Kimmy Rosielle, Annelotte van Haaps, Esther Kuijper, Nino Tonch, Disha Karim, Merel Oskam, Roos van den IJssel, Ben Willem Mol, Cornelis Lambalk, Kim Dreyer, Velja Mijatovic

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ABSTRACT

Study question: Is Virtual Reality (VR) an effective non-pharmacological tool to reduce procedural pain during hysterosalpingography (HSG)?

Summary answer: An HSG with VR does not reduce procedural pain scores compared to an HSG without VR.

What is known already: An HSG is often experienced as painful and uncomfortable. VR has been proven successful to reduce acute procedural pain during a variety of medical procedures and interventions.

Study design, size, duration: We performed a two-centre open-label randomized controlled trial between January 2021 and October 2022.

Participants/materials, setting, methods: Women scheduled for HSG as part of their infertility work-up were screened for participation. After informed consent, women were randomized between HSG with or without VR. Due to the nature of the intervention, the study was not blinded. VR was administered by a head-mounted device displaying nature movies and/or relaxation exercises. The primary endpoint was procedural pain measured using VAS (scale 0.0-10.0cm). Procedural pain was divided into overall pain score and peak pain score during the procedure. It was measured immediately after HSG. Secondary endpoints included patient satisfaction, VR preferences and adverse effects of VR.

Main results and the role of chance: We included a total of 134 women, 69 to the intervention group (HSG with VR) and 65 to the control group (HSG without VR). The mean VAS for peak pain was 6.80 cm (SD 2.25) in the intervention group versus 6.60 cm (SD 2.40) in the control group (mean difference 0.28 (95%CI -0.57, 1.12), P = 0.52). The mean VAS for overall pain was 5.00 cm (SD 2.10) in the intervention group versus 4.90 cm (SD 2.13) in the control group (mean difference 0.06 (95%CI -0.71, 0.84), P = 0.88). The expectation that VR would be a good distraction from pain during HSG was correlated with both overall and peak pain scores. When correcting for this expectation, we found that women in the intervention group reported significantly higher scores, both in peak (adjusted MD 0.58 (95%CI -0.81, 1.97), P = 0.021) and overall (adjusted MD 0.43 (95%CI -0.84, 1.71), P = 0.013) pain, compared to the control group. There were no differences in the prevalence of symptoms that were considered as adverse effects of VR.

Limitations, reasons for caution: The study was not blinded. Reasons for declining participation in the study were anxiety or wanting full control during HSG, which might have created selection bias. The distraction score possibly indicates that the level of VR immersiveness was not optimal due to the lack of sound and/or the type of VR applications. Future studies should investigate whether more immersive or interactive VR applications could decrease procedural pain scores during HSG.

Wider implications of the findings: Since Virtual Reality does not reduce procedural pain, this additional tool should not be used during HSG.

INTRODUCTION

Infertility affects roughly one in six couples worldwide with the prevalence ranging between approximately 12.6% and 17.5% of the adult population. In the Netherlands, 11.4% of women wishing to conceive suffer from infertility. This can significantly compromise quality of life [1-3]. The most common causes of infertility include tubal pathology and pelvic adhesions. Therefore, evaluation of the Fallopian tubes is essential as part of the fertility work-up, especially in patients with an increased risk for tubal pathology [4,5]. The traditional method for investigating tubal patency during fertility work-up is hysterosalpingography (HSG). During HSG, iodine-containing contrast is infused into the uterine cavity and subsequently into the Fallopian tubes. The contrast is visualized by fluoroscopy to determine whether it enters the abdominal cavity, indicating patency of the Fallopian tubes. HSG was initially introduced as a diagnostic test. However, a therapeutic effect has been proven in women with unexplained infertility, by increasing the chance of an ongoing pregnancy especially when oil-based contrast is used [6-8]. Despite this, HSG can cause discomfort and pain during and immediately after the procedure, with average reported pain scores ranging from 3.7 to 5.0 cm on the Visual Analogue Scale (VAS, scale 0.0-10.0 cm) [9-11]. The painful cramping sensations are caused by cannulation of the cervix with instruments, by distention of the uterine cavity due to infusion of contrast, by increasing the pressure in the Fallopian tubes, and by peritoneal irritation caused by contrast spillage into the abdomen [12]. Since the different parts of the female reproductive system are innervated by different pathways and nerves, targeting the overall pain with local analgesics is challenging [13]. Several regimens of analgesics have been studied using various routes of administration, e.g. oral, topical (a spray on the cervix or intrauterine installation with analgesics), locally injected, and intravenous administration of analgesics. A meta-analysis by Hindocha et al. showed that topical and locally injected analgesics can reduce the median pain score during the procedure, whereas the most obvious pain reduction was established by intravenous opioids. However, because of potential cardiorespiratory adverse effects, administration of intravenous opioids requires continuous monitoring, making this a not attractive method of pain management to apply during HSG. In addition, it is important to note that the quality of evidence in the study was low to very low [12].

Virtual Reality (VR), a non-pharmacological intervention, has been introduced in medical practice in the past couple of years and is increasingly used to reduce pain and anxiety. It creates a distraction from the present and diverts attention away from physical sensations by taking the user into a 3-dimensional virtual world, usually without any major adverse effects [14]. VR for medical use has been proven successful in decreasing acute pain during different medical procedures and interventions, including a reduction in procedural pain during office hysteroscopy and episiotomy repair [15-17]. During office hysteroscopy, similar medical instruments are used as during HSG. A speculum is inserted, after which a hysteroscope is inserted through the cervical canal, and fluid is used to achieve dis-

tention of the uterine cavity [18]. However, it is possible that during HSG more pain can be experienced compared to that during hysteroscopy. This is because, during HSG, the fluid travels from the uterine cavity, through the Fallopian tubes into the abdominal cavity whereas during hysteroscopy the fluid remains in the uterine cavity. This can result in larger quantities of fluid infusion during HSG, and therefore larger pressure build-up. Nonetheless, pain experienced during both procedures is considered mild to moderate in severity [19]. It is therefore possible that VR could also be considered effective in reducing pain during HSG. This hypothesis is confirmed by a recently published study where VR was found effective in reducing pain during HSG. This study was performed with a small sample size (62 participants) which was based on a small aimed effect size (0.88). In addition they did not provide any pain medication during HSG [20].

Aside from targeting pain, VR can also lead to lower stress scores [21,22] and anxiety scores [20,23] as well as higher satisfaction scores during medical procedures [20,24]. Considering these favourable outcomes of VR on the perception of procedural pain, we hypothesized that the application of VR could reduce pain during HSG in infertile patients. Therefore, the aim of this study is to investigate whether VR is an effective non-pharmacological method to reduce pain during HSG in women undergoing infertility workup.

METHODS AND MATERIALS

Study design

This randomized controlled trial (RCT) was performed in one university hospital, with two locations, and one teaching hospital in the Netherlands. The study was approved by the institutional review board of the Amsterdam UMC, location VUmc (reference number 2020.0687). The trial was prospectively registered in the Dutch trial register (http://www.trialregister.nl ; registration number NL9203).

Participants

All women referred for HSG were screened for eligibility. Women were eligible for study participation if they were evaluated for infertility and had sufficient knowledge of the Dutch or English language to read and understand the patient information sheet. Women were excluded from study participation if they had a history of surgery to the cervix, if they had undergone an HSG before, if they had a known allergy to iodinated contrast, or if they currently used antidepressants, sedatives, or analgesics on a daily basis.

Randomization

After providing written informed consent, participants were randomized between the HSG with VR (intervention) group or HSG without VR (control) group. Randomization was performed in a 1:1 ratio with variable block sizes varying from four to eight using

the web-based system Castor (Castor Electronic Data Capture, Ciwit BV, Amsterdam, the Netherlands) and stratified per centre. Due to the nature of the intervention, blinding of participants and physicians was not possible.

Study procedures

The HSG was performed according to local standard procedure protocols. It was scheduled in the follicular phase of the menstrual cycle after cessation of menstrual bleeding, or after cessation of progesterone induced bleeding in case of amenorrhea. According to local protocols, all women were advised to take non-steroid anti-inflammatory drugs such as naproxen or ibuprofen as pain management the evening before and 2h before HSG. During the procedure, the patient was placed in lithotomy position after which a speculum was inserted. The cervix was cannulated with a cervical vacuum cup, a metal cannula (hysterophore) or an HSG balloon catheter, depending on the preference of the physician performing HSG and local availability. During infusion of approximately 10 ml of oil-based (Lipiodol Ultra Fluid®, Guerbet, Villepinte, France) or water-based (iodixanol, Visipaque®, General Electric Healthcare, Buc, France) contrast medium, four to six radiographs were obtained. The radiographs were examined by a gynaecologist and/or radiologist to evaluate the patency of both Fallopian tubes according to local protocols. Participants assigned to the intervention group were given a short instruction of the VR headset prior to the HSG procedure. After meeting their physician and getting into lithotomy position on the radiology table, women placed the VR headset over their eyes. Participants were asked to wear the VR headset during the entire procedure, until all instruments were removed. Sound from the VR headset was switched off to enable participants to communicate with the physician performing the procedure at all times. A dedicated researcher was present during the entire procedure for technical support with the VR system. In case of complaints or potential adverse events of the VR headset, the participants were able to adjust or remove the headset themselves or ask for assistance from the dedicated researcher.

VR Technology

The VR headset and software used in this study were CE-certified and obtained from SyncVR (SyncVR Medical B.V., Utrecht, the Netherlands). The head-mounted PICO G2 4K device (Pico Interactive Inc., San Francisco, USA) included a VR headset and a remote control (Fig.1a). Participants were able to navigate the VR headset on their own using the remote control. However, if they felt unsure navigating the system, the researcher was able to take over control of the VR headset on a hand-held device. SyncVR Relax & Distract is a software module installed on the VR headset which enables patients to choose between approximately 20 relaxing movies and breathing exercises, all designed for use in medical practice (Fig. 1). Games, requiring movement of the participant, and movies with an element of surprise were removed from the library to decrease the chance of sudden

movements during the HSG. It was thought that sudden movements were undesirable and unsafe for participants.



Figure 1. Virtual Reality (VR) intervention and the installed VR applications. The VR applications were provided by SyncVR. (A) The head-mounted VR device (PICO G2 4K) with remote control. (B) Example of the nature movies. (C) Example of the breathing exercises.

Outcomes

The primary outcome of this study was procedural pain during HSG, divided into overall pain and most severe pain that participants experienced. Pain was measured using a VAS ruler (scale 0.0-10.0 cm) immediately after HSG. Secondary outcomes included use of oral analgesics within the first 24 hours following HSG, VR experience and satisfaction, and VR-related adverse events (nausea, dizziness, headache, blurry vision). The anxiety level, VR expectations prior to HSG, and HSG-procedure characteristics were considered as possible confounding factors.

Data collection

Three questionnaires were distributed over the course of the study. First, all participants received a short questionnaire, usually distributed before randomization was performed, with an adapted version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS; N. Moerman, F.S.A.M. van Dam, M.J. Muller, and J. Oosting) to determine their level of anxiety prior to the procedure. It additionally contained questions regarding their usage of oral analgesics prior to the procedure. In the second questionnaire, distributed

immediately after the HSG procedure, participants were asked to score their overall pain level and their highest level of pain during the HSG procedure using a VAS-ruler (0.0-10.0 cm). The second questionnaire additionally contained questions on possible VR-related adverse events and evaluated participant satisfaction with the procedure. Participants in the intervention group received questions on their satisfaction with their chosen VR application. All questions used a 5-point Likert scale ranging from 1-5, where 1 represented 'not at all' and 5 represented 'completely/all the time'. During the conduct of the study, both the first and second questionnaire were extended. The added questions inquired on VR expectations and expected preferences for the VR software before the procedure. These questions were distributed to women in both the intervention and control group. The second questionnaire was extended with questions on VR experiences after the procedure. Only women in the intervention group received the questions regarding VR experiences.

The final questionnaire was sent by email using Castor EDC to all participants 24h after the HSG procedure. This last questionnaire inquired on adverse events or complaints, willingness to undergo the procedure again, and use of oral analgesics within the first 24h after the procedure. All questionnaires can be found in the Supplementary Data File S1. Finally, medical details from the HSG procedure (e.g. the type and volume of contrast medium used, instrument used for instalment of contrast) and results of the HSG were collected from the electronic patient files.

Statistics

All data were analysed using IBM SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics were presented using descriptive statistics with medians and interquartile ranges for non-normally distributed continuous variables, and with a mean and standard deviation (SD) for normally distributed continuous variables. Categorical variables were presented as absolute numbers and percentages. Continuous outcomes were analysed with the use of an independent t-test or the Mann-Whitney U-test as appropriate, whereas categorical variables were analysed with use of the chi-square test or the Fishers exact test. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Anxiety level, VR expectations and use of analgesics were analysed as possible confounders prior to the procedure. The used instruments during HSG, type of contrast used and HSG outcomes were analysed as possible confounders during HSG. A multiple linear regression model was fitted to assess the influence of the predefined confounders on the primary outcome measures. The significant confounders were subsequently used in an ANCOVA test to compare group means while controlling for the effects of these confounders.

Sample size

Based on previous research in a similar, Dutch population, we anticipated an overall pain score of 5.0 cm (in VAS, scale 0.0-10.0 cm) in the control group [6]. We considered a reduction of 1.5 cm and a SD of 1.7 cm in pain score to be clinically relevant, which resulted in a calculated sample size of 134 women (67 in each group) with an obtained power of 80%, an alpha of 0.05, and a loss to follow-up rate of 5% using PASS (15.0.5).

RESULTS

Between January 2021 and October 2022 a total of 211 women were screened for eligibility, of whom 140 women provided informed consent. We randomly allocated 71 women to HSG with VR (intervention group), and 69 to HSG without VR (control group). Five women ultimately did not meet the inclusion criteria and one woman did not undergo an HSG leading to missing data with regards to our primary endpoints. This meant that there were 69 women in the intervention group, and 65 women in the control group (Fig. 2).

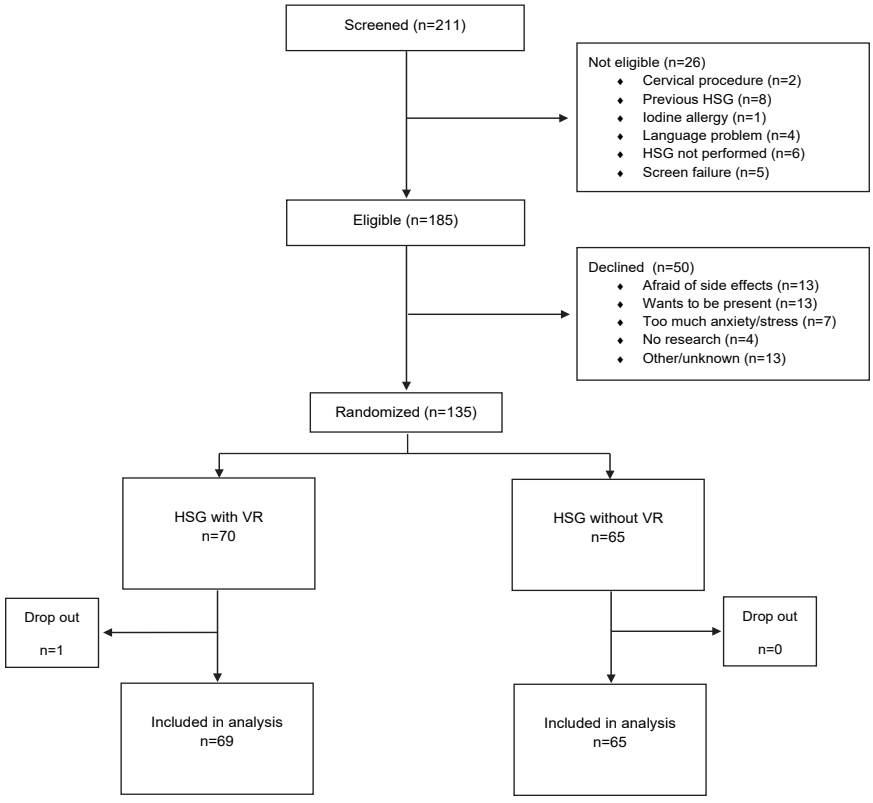

Figure 2. Flow chart of inclusions.

The two groups were similar in terms of baseline characteristics, except for the anxiety score prior to HSG which was 9.2 (SD 2.3) in the intervention group and 10.1 (SD 2.4) in the control group (APAIS range 3.0 to 15.0, p=0.018). Bilateral tubal patency was seen in 52 out of 69 women in the VR group and in 52 out of 65 women in the non-VR group. All other baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics and HSG procedure details of all participants.

Characteristic		Intervention n= 69	Control n= 65	P-value
Age (year) (median (IQR))		35 (5.00)	35 (4.00)	
BMI (kg/m^2) (mean (SD))		23.9 (4.4)	24.6 (4.4)	
Duration of infertility (months) (mean (SD))		29.8 (15.4)	27.0 (16.4)	
Primary infertility (%)		47 (72.3)	45 (65.2)	
Risk assessment for tubal pathology[1] (%)				
	High risk	11 (15.9)	12 (18.5)	
	Low Risk	58 (84.1)	53 (81.5)	
Cause of infertility (%)				
	Male factor	7 (10.1)	5 (7.7)	
	Female factor	12 (17.4)	7 (10.8)	
	Male and female factor	1 (1.4)	2 (3.1)	
	Unexplained	49 71.0)	51 (78.5)	
Current smoker (%)		3 (4.3)	4 (6.3)	
Pain medication used prior to HSG (%)		65 (94.2)	62 (95.4)	
Type of pain mediation used (%)[2]				
	Paracetamol/Panadol	18 (36.5)	12 (18.5)	
	NSAIDs[*4]	54 (78.3)	56 (86.2)	
	Opioids	0	0	
	Other	0	1 (1.5)	
Mean Anxiety score (APAIS) (mean (SD))		9.2 (2.3)	10.1 (2.4)	0.018
Type of HSG instruments				
Cervical vacuum cup		42 (60.0)	41 (63.1)	
Hysterophore		5 (7.2)	4 (6.1)	
Balloon catheter		18 (26.0)	18 (27.7)	
Multiple		4 (5.8)	2 (3.1)	
Type of contrast (%)				
Oil-based		66 (95.7)	61 (93.8)	
Water-based		3 (4.3)	4 (6.2)	
Tubal patency (%)				
Bilateral tubal patency		52 (75.4)	52 (80.0)	0.481

Table 1. Baseline characteristics and HSG procedure details of all participants. (*continued*)

Characteristic	Intervention n= 69	Control n= 65	P-value
Unilateral tubal patency	15 (21.7)	9 (13.9)	
No tubal patency	2 (2.9)	1 (1.5)	
Unknown[3]	0 (0)	3 (4.6)	

HSG, hysterosalpingography; NSAIDs, non-steroidal anti-inflammatory drugs; APAIS, the Amsterdam Preoperative Anxiety and Information Scale (measured on a scale of 3–15).

[1] Considered as high risk for tubal pathology were history of symptomatic Chlamydia Trachomatis infection, a positive chlamydia antibody test (CAT) on screening, history of Pelvic Inflammatory Disease (PID), history of endometriosis, history of surgery on ovaries or fallopian tubes, and a history of ectopic pregnancy.

[2] Some patients used multiple types of pain medication.

[3] HSG could not confirm bilateral tubal patency, e.g. because the HSG was stopped prematurely due to intravasation.

Worst and average pain during HSG

Women in the intervention group reported similar mean overall pain scores compared to women in the control group, with a score of 5.0 cm (SD 2.10) versus 4.9 cm (SD 2.13), respectively (mean difference (MD) 0.06 (95%CI 0.71, 0.84, p=0.88). In addition, women in the intervention group reported a mean peak pain score of 6.8 cm (SD 2.25) whereas women in the control group reported a mean peak pain score of 6.6 cm (SD 2.40) (MD 0.28 (95%CI -0.57, 1.12), p=0.52). There was no significant difference in time spent thinking about pain, between the intervention and control group (Table 2).

Table 2. Primary outcome.

Outcome	Intervention (n=69)	Control (n=65)	Mean difference (95% CI)[1]	P-value[2]
Overall pain (VAS) (mean (SD))[3]	5.0 (2.10)	4.9 (2.13)	0.06 (-0.71 – 0.84)	0.876
Peak pain (VAS) (mean (SD))[3]	6.8 (2.25)	6.6 (2.40)	0.28 (-0.57 – 1.12)	0.519
Time spent thinking about pain (mean (SD))[4]	3.3 (0.99)	3.5 (1.10)		0.159
Pain medication used within 24h after HSG (%)[5]				0.360
Yes	9 (18.8)	10 (21.3)		
No	37 (77)	37 (78.7)		
Unknown	2 (4.2)	0		

Table 2. Primary outcome. (*continued*)

Outcome	Intervention (n=69)	Control (n=65)	Mean difference (95% CI)[1]	P-value[2]
Type of pain medication used (%)[6]				
Paracetamol	3 (33.3)	6 (60)		0.317
NSAIDs	8 (88.9)	6 (60)		0.779

Pain scores (in VAS) immediately after HSG, measured in peak pain and overall experienced pain.
[1] Statistics with use of the independent samples t-test.
[2] Statistics with use of the Fisher's exact test or chi-square test.
[3] Measured using a VAS-ruler, scale 0.0–10.0 cm.
[4] Reported for n = 68 intervention group, n = 63 control group, measured using a 5-point Likert scale.
[5] Reported for n = 48 intervention group, n = 47 control group.
[6] Reported for n = 65 intervention group, n = 62 control group

Several factors were studied as confounding factors for the peak and overall pain scores, including the expectation that VR would provide distraction or pain relief, pre-HSG anxiety levels, tubal patency, instrument type, contrast medium usage or prior VR experience (Supplementary Table S1). Since overall pain scores were notably affected by the expectation that VR would be an effective distraction tool, reported by 44 out of 57 women who were asked on their VR expectation, both peak and overall pain scores were adjusted for this influence. When adjusting for expected distraction, we found significant higher pain scores in the intervention group, compared to the control group. This was seen both in peak pain scores (adjusted MD 0.58 (95%CI -0.81, 1.97), p=0.021) and in overall pain scores (adjusted MD 0.43 (95%CI -0.84, 1.71), p=0.013) (Table 3).

Table 3. Adjustment of peak and overall pain scores for the expectation of distraction, calculated using ANCOVA.

Covariate	Adjusted mean (SD)				Mean difference (95% CI)		P-value	
	Peak pain score		Overall pain score		Peak pain score	Overall pain score	Peak pain score	Overall pain score
	Intervention	Control	Intervention	Control				
Expect distraction	7.03 (0.45)	6.45 (0.50)	5.31 (0.41)	4.88 (0.46)	0.58 (-0.81, 1.97)	0.43 (-0.84, 1.71)	0.021	0.013

VR experience

A subset of women (n=57) received an additional questionnaire. To the women who received VR during HSG (n=30), questions were asked about their VR experience. All scores were measured on a 5-point Likert scale (scale 1-5). These women reported a mean score of 3.2 (SD 0.84) on being able to concentrate on the VR application and mean score of

3.5 (SD 0.76) on feeling distracted from the medical procedure by VR (Table 4). Women reported missing sound from the VR intervention with a mean score of 2.5 (SD 1.30). In total, 60% (18/30) of women in the subset that had received VR reported that their expectations regarding VR were fully met. As for the participants whose expectations were only partially met (11/30) or not met at all (1/30), they most frequently mentioned that pain predominated over VR or that the videos were insufficiently engaging.

Table 4. Virtual Reality (VR) experiences.

VR experiences	Total n=30[1]
Distracted by VR (mean (SD))	3.54 (0.76)
Able to concentrate (mean (SD))	3.19 (0.94)
Feeling into the VR environment (mean (SD))	2.90 (1.14)
Missing sound (mean (SD))	2.50 (1.30)
Satisfaction with film options (%)	14 (53.8)
VR expectations were met (%)	
Yes	18 (60.0)
No	1 (3.3)
Partially	11 (36.7)

Full questions (range 1–5, 'not at all' to 'completely/all the time'): 'To what extend did the movie(s) distract you from the HSG?' 'To what extend were you able to focus on the movie(s)?' 'There was no sound with the movie(s). Did you miss this?'.

[1] These questions were answered by women from the subset (n = 57) that had received the VR intervention (n = 30).

Patient satisfaction and adverse effects

Satisfaction

Both women in the intervention group and in the control group reported comparable mean satisfaction scores on a 5-point Likert scale (4.1 (SD 0.84) vs. 3.8 (SD 1.02) respectively, P=0.20). Moreover, women in the intervention group expressed a similar willingness to undergo another HSG with VR compared to the control group (3.4 (SD 1.35) vs. 3.6 (SD 1.37) respectively, P = 0.61). However, women in the intervention group indicated significantly lower willingness to undergo another HSG without VR compared to women in the control group (2.7 (SD 1.25) vs. 3.6 (SD 1.38) respectively, P = 0.01) (Table 5).

Table 5. Patient satisfaction.

Outcome	Intervention n=30	Control n=27	p-value
Satisfaction score (mean (SD))	4.12 (0.86)	3.78 (0.90)	0.197
Another HSG with VR (mean (SD))	3.43 (1.35)	3.61 (1.37)	0.608
Another HSG without VR (mean (SD))	2.73 (1.25)	3.63 (1.38)	0.005
Advise an HSG with VR to others (mean (SD))[1]	4.23 (0.91)	N/A	

HSG, hysterosalpingography. Full questions (range 1–5): 'How satisfied are you with the HSG with/without VR?' 'Would you be willing to undergo another HSG without VR?' 'Would you be willing to undergo another HSG with VR?' 'Would you advise to use VR if someone else had to undergo HSG?'. All measured using a 5-point Likert scale (scale 1–5).

[1] Only answered by women in the VR group

Adverse effects

There was no significant difference in symptoms that have been described as side effects from VR between women in the intervention group and in the control group (Supplementary Table S2). Seven patients removed the VR headset during the procedure. The reported reasons were discomfort (three patients), being nauseous (one patient), and too much pain from the procedure (three patients).

DISCUSSION

This RCT showed that the use of VR during HSG did not reduce peak pain and overall pain. The expectation that VR would offer a distraction from HSG related pain was found to be a confounding factor. After correcting for this confounder, significantly higher overall pain scores and peak pain scores were seen in the intervention group, compared with the control group. On the other hand, women receiving VR during HSG were significantly less willing to undergo a future HSG without VR than women not receiving VR.

Our study has several strengths. Patients were recruited from two locations of a university hospital as well as a non-academic teaching hospital, ensuring a diverse patient population. In addition to collecting pain scores, we included several confounding factors to study whether this might have affected experienced pain. Our study also has some limitations. A significant number of eligible women (50/185) declined participation in this study, potentially introducing a selection bias. Additionally, VR immersiveness was relatively low in the intervention group due to the absence of sound. According to previous studies, this might have reduced interactivity while this is known to enhance immersion and attentional involvement [25-27]. Finally, there is a possibility that a placebo effect, nocebo effect, or Hawthorne effect could have influenced pain scores [28,29]. Because a randomized design was chosen for this study, we assume that this effect would have

occurred equally in both groups which is confirmed by the fact that we found similar pain scores in both groups.

VR has been found to be effective in pain and/or anxiety management during labour [30-33]. However, in gynaecological procedures other than labour the evidence is limited. Regarding the appliance of VR in (outpatient) gynaecological procedures, the results of our study are in line with the RCT by Fouks et al. (2022) where VR was applied during office hysteroscopy [34]. They applied a similar VR intervention to ours, but with the addition of background sounds. VR did not result in lower pain scores during the procedure (median pain score 5.0 (NRS, range 0.0-10.0) in the intervention compared to the control group, P = 0.67). Contrary to our results, a recently published study applying VR during HSG found that women receiving VR reported significantly less pain during HSG, compared to the control group (1.81 versus 3.55, P = 0.02) [20]. They incorporated relaxing background music to the VR intervention. However, they excluded patients with procedural difficulties during HSG or VR discontinuation which may have introduced bias. Additionally, women did not receive any analgesics prior to HSG, whereas in our study 95% of participants used oral analgesics prior to HSG. Therefore, the effect of VR on pain reduction in our study could be too small to exceed the effect of the oral analgesics taken by most participants. However, a previous systematic review by Mallari et al. (2019) contradicts this as they stated VR was more effective when added to analgesics [35].

Significant pain reduction was also seen in the study by Deo et al. (2021) where VR was applied during (outpatient) hysteroscopy (mean average pain 3.7 (SD 2.66) in the intervention group vs 6.0 (SD 2.62) in the control group, numeric rating scale 0.0-10.0, p = 0.01) and in the study by JahaniShoorab et al. (2015) where VR was applied during episiotomy repair (mean VAS 9.0 mm (SD 12.6) vs 23.6 mm (SD 19.8), VAS 0.0-100.0 mm, P = 0.04) [17,36]. There are several explanations for the lack of effect in the reported pain scores in our study. One possibility is that the high expectations for VR to alleviate HSG-related pain by distraction were not met. Despite the randomized design of this study, it is possible that pain scores of women receiving VR during HSG were more influenced by the expectation that VR reduces pain, compared to women not receiving VR during HSG. This hypothesis is confirmed by the fact that, after correcting the pain scores for these expectations, pain scores were significantly lower in the control group. In addition, by disabling sound and interactive games, VR immersion was reduced, and this is now acknowledged to be an important contributing factor to successful pain reduction by VR application [25,26]. Finally, HSG can be more painful in women with tubal blockage, since this prevents outflow of contrast, therefore leading to intrauterine pressure build-up [37]. However, the prevalence of bilateral tubal blockage in our study was very low in both groups and was not statistically significant confounding factor.

This study suggests that VR was not beneficial in terms of pain reduction during HSG. However, other studies regarding this subject have found a positive effect of VR on pain. Therefore, it is possible that only certain subgroups of patients could benefit from VR during gynaecological procedures, rather than all patients undergoing the procedure. In future studies, it could be beneficial to perform more research into the mechanism of action of VR in the field of Gynaecology and Reproductive Medicine. This way, subgroups of patients who would or would not benefit from VR can be identified. Distinguishing factors could be different coping strategies, e.g. wanting to have full control or wanting to be 'absent' during the procedure, or different levels of anxiety before the procedure. In conclusion, VR does not reduce procedural pain experienced during HSG. More importantly, women who expected VR to distract them during HSG experienced more pain.

QR code to article for supplementary materials



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Chapter 4

No anxiety and pain reduction by Virtual Reality during oocyte retrieval in IVF/ICSI treatment: results of a randomised controlled trial.

Annelotte van Haaps, Anneke Schreurs, Kimmy Rosielle, Velja Mijatovic, Jan Willem Kallewaard, Kim Dreyer

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ABSTRACT

Study question: What is the effect of Virtual Reality (VR) on anxiety and pain during oocyte retrieval in IVF/ICSI treatment?

Summary answer: There is no significant effect of VR on anxiety and pain during oocyte retrieval in IVF/ICSI treatment.

What is known already: Patients undergoing oocyte retrieval in IVF/ICSI treatment often experience anxiety and pain, despite conscious sedation. VR might offer a solution since it has been successful in reducing procedural anxiety and pain during medical procedures, with the potential to replace standard analgesic care.

Study design, size, duration: A single-centre, open-label, randomized controlled trial was conducted between February 2023 and August 2024. Due to the nature of the intervention, the study was not blinded.

Participants/materials, setting, and methods: Patients undergoing oocyte retrieval as part of IVF/ICSI treatment were screened. After providing informed consent, participants were randomized between oocyte retrieval with VR added to conscious sedation and oocyte retrieval with conscious sedation only. When assigned to the intervention group, patients received the VR intervention through a head-mounted device, showing nature films and relaxation exercises. This was added to standard care which includes analgesia and sedatives. Sounds were delivered through the head-mounted device or headphones. The primary outcome was pre- and post-procedural anxiety, measured using the STAI questionnaire. Secondary outcomes included procedural pain (NRS, scale 0-10), satisfaction scores (NRS, scale 0-10), VR preferences, and side effects.

Main results and the role of chance: There were 113 participants included: 57 in the intervention group receiving VR and 56 in the control group not receiving VR. We observed no differences between intervention and control in pre-procedural anxiety (mean difference (MD) 0.14 (95% CI -1.78, 2.05), p=0.885), post-procedural anxiety (MD 0.45 (95% CI -1.21, 2.11), p=0.589), overall pain (MD -0.12 (95% CI -0.97, 0.73), p=0.779) and peak pain (MD 0.59 (-0.51, 1.68), p=0.287).

Limitations, reasons for caution: VR might only be effective for a certain group of patients undergoing retrieval, or might be more effective in reducing pre-procedural anxiety, which in turn might lead to a reduction in procedural pain. Furthermore, it might reduce pain up to a certain threshold, or be effective when the duration of the procedure is short.

Wider implications of the findings: Since VR does not affect anxiety and pain for the general patient population undergoing oocyte retrieval, we do not advise incorporating VR to standard IVF/ICSI anxiety and pain management. For future studies, it is important to investigate which subgroup could benefit from VR and how it could be implemented to study interventions from a non-pharmacological approach. Patient preferences regarding anxiety and pain management during IVF/ICSI treatment should be considered.

INTRODUCTION

Infertility is defined by the World Health Organization as the inability to conceive after 1 year of unprotected intercourse and affects one in six couples in the Netherlands [1]. It can be caused by various factors or remain unexplained. Where female infertility can result from premature ovarian insufficiency, polycystic ovary syndrome, uterine fibroids or endometrial polyps, endometriosis or a tubal factor, male infertility can result from (post-) testicular deficiencies leading to reduced semen quality [2,3]. Depending on the cause of infertility, treatment methods like IVF or ICSI can be applied [4,5]. With IVF/ICSI treatment, multiple mature oocytes (follicles) are induced by performing ovarian stimulation with gonadotropins. The oocytes are collected by aspiration of the follicles through an ultrasound-guided transvaginal puncture, which is known to cause anxiety and pain [4,6,7]. Turner et al. assessed anxiety levels during all phases of an IVF cycle using the State-Trait Anxiety Inventory (STAI, scale 20-80) and found mean State Anxiety (STAI-S) scores of 41.63 before oocyte retrieval [8,9]. With regards to pain during oocyte retrieval, the recent study by Buisman et al. found pain scores between 3.7 and 5.6 (in Numeric Rating Scale (NRS), scale 0-10), depending on the type of pain management [10]. Pain is thought to result from needle passage through the vaginal wall, peritoneum, and ovarian capsule, but can be experienced up to several days after oocyte retrieval [11,12]. Both procedural anxiety and pain can negatively affect patient satisfaction which, in turn, is thought to strongly influence therapy compliance, prognosis, utilization of healthcare and malpractice litigation [13-16]. Moreover, Schaller et al. found that IVF/ICSI treatment caused a significant psychological burden on couples, especially women, leading to premature treatment discontinuation [17]. This underlines the importance of providing adequate psychosocial support throughout treatment and optimizing anxiety and pain management.

There is a large variety of medication protocols that are used for anxiety and pain management in Dutch IVF clinics. The three most frequently used analgesia protocols include intravenously (IV) administered opioids, intramuscularly (IM) administered opioids, and non-sedative oral analgesics. Roest et al. found that 61% of IVF clinics have added benzodiazepines to their analgesics to reach a state of conscious sedation where anxiety and pain are sufficiently managed but patients are responsive and able to communicate with the healthcare provider, breathe on their own, and maintain their natural psychological reflexes [18]. This makes it a relatively effective and safe option. However, anxiety and pain may not be fully alleviated, making an additional non-pharmacological therapeutic option necessary [6,19,20]. Although traditional distraction methods can be helpful, more effective and low-risk alternatives are needed [21]. Virtual Reality (VR), initially introduced in 1994 for surgical simulation and medical training, could offer a solution. It distracts the patient by immersing them in a virtual environment resulting in competition between limited shared attentional resources and incoming nociceptive signals. This ultimately leads to reduced (procedural) anxiety and pain, resulting in VR being increasingly used

as a successful method to reduce procedural anxiety, and as an adjunct or alternative to pharmacologic analgesia and sedation for a wide range of medical procedures [22-24]. Studies within the field of gynaecology found it effective in reducing anxiety, pain, or both during hysteroscopy, hysterosalpingography (HSG), episiotomy repair, and intra-uterine device insertion [25-31]. Furthermore, Chan et al. found that VR significantly reduced anxiety and depressive symptoms, when provided prior to gynaecological procedures [25,32].

To our knowledge, the use of VR during oocyte retrieval has not yet been studied [33]. Therefore, in this study, we aim to determine the effect of VR on anxiety and pain during oocyte retrieval in IVF/ICSI treatment, thereby enhancing patient satisfaction.

METHODS AND MATERIALS

Study design

This randomized controlled trial was performed at the Department of Reproductive Medicine of the Amsterdam UMC location VUmc between February 2023 and August 2024. The study was approved by the Amsterdam UMC institutional review board and prospectively registered at clinicaltrials.gov (reference number NCT05555498).

A sample size was calculated. Our study aimed for an 8-point reduction in anxiety (in STAI, scale 20-80) with an SD of 14, which was based on the study by Turner et al. (2013) [9]. The desired statistical power was 80% with an alpha of 0.05 and a 10% loss to follow-up rate. This resulted in a calculated sample size of 112 participants. All patients undergoing oocyte retrieval as part of IVF/ICSI treatment were screened for eligibility. We included patients aged between 18 and 43 years old who were undergoing their first, second, or third oocyte retrieval, in the hopes of becoming pregnant. They had to be proficient in English or Dutch language. Patients were excluded if they: used antidepressants, sedatives, or analgesics daily, were undergoing oocyte retrieval because of fertility preservation, had a visual or auditory impairment, suffered from technology-related sensitivity (dizziness, epilepsy, nausea, motion sickness), or were unwilling or unable to provide informed consent. Patients were provided with study information by their treating physician. At least 1 week after they were provided the information, patients were contacted by the researcher involved in the study to answer any questions. They were then asked about study participation. Prior to oocyte retrieval, participants were asked to sign their informed consent form, after which they were randomized to the intervention group (oocyte retrieval with conscious sedation and VR) or the control group (oocyte retrieval with conscious sedation but without VR). Randomization was performed by the researcher involved in the study. Participants were told the outcome of randomization prior to their oocyte retrieval. Randomization was performed using Castor (Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands) in a 1:1 ratio and using variable block sizes of 4-8.

Study procedures

According to standard local protocol, patients were instructed to arrive at the IVF centre an hour before oocyte retrieval. During this hour, anxiety and pain medication was administered to both the intervention and control group. This consisted of conscious sedation with IM opioids (pethidine or morphine) for pain reduction and oral benzodiazepines (midazolam or diazepam) for anxiety reduction. During the procedure, the participant was placed in a lithotomy position after which the speculum was inserted and the vaginal wall was cleaned. After the speculum was removed, the sterile ultrasound probe with a needle guide was inserted and a hollow needle was inserted into this guide. Under direct ultrasound guidance, the needle punctured the vaginal wall to reach the ovaries. Each follicle was punctured, and the oocyte fluid was aspirated and sent to the laboratory to isolate the oocytes. From start to finish, the procedure usually lasts between 20 and 30 min. Apart from the medical staff, one partner or support person was allowed in the room with the participant.

When participants were assigned to the intervention group, they were given instructions on the VR headset in the hour before retrieval, where they could look through all applications installed on the headset. During the procedure, participants received the eye-covering headset after the vaginal wall was cleaned and speculum removed. Sounds were delivered through the headset itself or headphones connected to the headset depending on personal preference. In case of complaints or adverse events, the headset could be removed. When permitted by the participant, a dedicated researcher was present at all times for technical support with the VR intervention.

Virtual Reality technology

A CE-certified VR headset was used with software from SyncVR (SyncVR Medical B.V., Utrecht, The Netherlands) installed on the headset. The head-mounted PICO G2 4K device (Pico Interactive Inc., San Francisco, United States of America) included a VR headset and remote control. When participants needed assistance, the researcher was able to take over control of the headset using a handheld device. The SyncVR Relax and Distract software was installed on the VR glasses, which is designed to be used in a medical setting and offers approximately 40 VR interventions. The software includes relaxing nature films and breathing exercises consisting of 3D visualization and accompanying sounds. Participants were able to navigate through the software installed on the VR glasses and choose a nature film or breathing exercise they found most appealing. Although the software is developed for pain management during medical procedures, it was not tailored to oocyte retrieval specifically nor personalized for each individual participant. Interactive games were removed from the VR library to prevent sudden movements during the oocyte retrieval because this was considered undesirable and unsafe for participants. Sounds could be delivered either through headphones connected to the VR glasses or

through the VR headset itself. The participants could choose whether they wished to add headphones.

Outcomes

The primary outcome focused on the difference in anxiety experienced before and immediately after oocyte retrieval (measured using the STAI-S questionnaire). Secondary outcomes included the difference in general anxiety before and 72h after oocyte retrieval (measured using the STAI-T questionnaire), the difference in procedural pain during oocyte retrieval (in NRS, scale 0-10) between the intervention and control group, which was divided into overall and peak pain scores, pain during the first 72h after retrieval (in NRS), as well as patient and healthcare provider satisfaction scores (in NRS), experienced side effects, VR expectation, and satisfaction with VR (for the intervention group).

Data collection

All data were stored using Castor EDC. Baseline characteristics were collected through the electronic patient file where age, duration of infertility, IVF/ICSI cycle number, and vital parameters before and after retrieval were obtained. Healthcare providers were asked to register their procedural satisfaction scores in the patient file, which were also collected. All other data were collected using three sets of questionnaires. Two questionnaires were distributed on paper before and immediately after oocyte retrieval, while the third set was distributed digitally 72h after the procedure. The first set of questionnaires, distributed before medication administration to minimize confounding bias, included questions about the participants' VR expectations but also the State Trait Anxiety Inventory-State (STAI-S) and State Trait Anxiety Inventory-Trait (STAI-T) questionnaire. The STAI questionnaires were developed by Spielberger et al. and are validated measurement tools to quantify stress [8]. The STAI-S is used to measure the experienced stress 'right now' while the STAI-T questionnaire is used to measure stress 'in general'. Ultimately, a score between 20 and 80 can be calculated, where a score between 20 and 39 is seen as 'little perceived stress', a score between 40 and 59 is 'average perceived stress' and a score between 60 and 80 is 'high perceived stress'. The second set of questionnaires, distributed within 10 min after oocyte retrieval, included the STAI-S to quantify procedural stress. In addition, patients were asked to score their procedural overall pain and peak pain (both in NRS, scale 0-10), their procedural satisfaction (in NRS, scale 0-10), and whether they experienced any side effects. When assigned to the intervention group, participants were also asked about their VR experiences. Finally, the third set of questionnaires was distributed digitally 72h after oocyte retrieval. It included the STAI-T questionnaire and questions assessing experienced pain and analgesics use in the first 72h after retrieval.

Statistical analysis

Data were analysed according to the intention-to-treat principle using IBM SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented

with mean and SD for normal distributed data and median with interquartile ranges for non-normal distributed data. Categorical baseline characteristics were presented as absolute numbers and percentages. Differences in anxiety and pain scores between the intervention and control group were studied using the independent samples t-test in case of normally distributed data and the Mann-Whitney-U test in case of non-normally distributed data. Data distribution was tested by drafting a histogram of the variable in question. Ordinal data were analysed using the Pearson chi-square test. Finally, possible interactions, which were compiled during data analysis, were studied using simple linear regression. These were mostly based on a previous study where we studied the effect of VR on pain during HSG [34]. We studied possible interactions between anxiety, pain and the number of punctured follicles, age, unilateral or bilateral punction, dosage and type of medication, duration of the procedure, IVF/ICSI cycle number, expectations prior to the procedure and VR experiences. Finally, we studied whether there was a possible interaction between the experienced anxiety and procedural pain.

RESULTS

A total of 275 patients were screened for eligibility, of whom 120 provided informed consent. Ultimately, seven participants did not proceed with oocyte retrieval or withdrew consent after randomization, leading to 57 participants in the intervention group and 56 in the control group being analysed (Fig. 1). Baseline characteristics are presented in Table 1, which showed no significant differences.

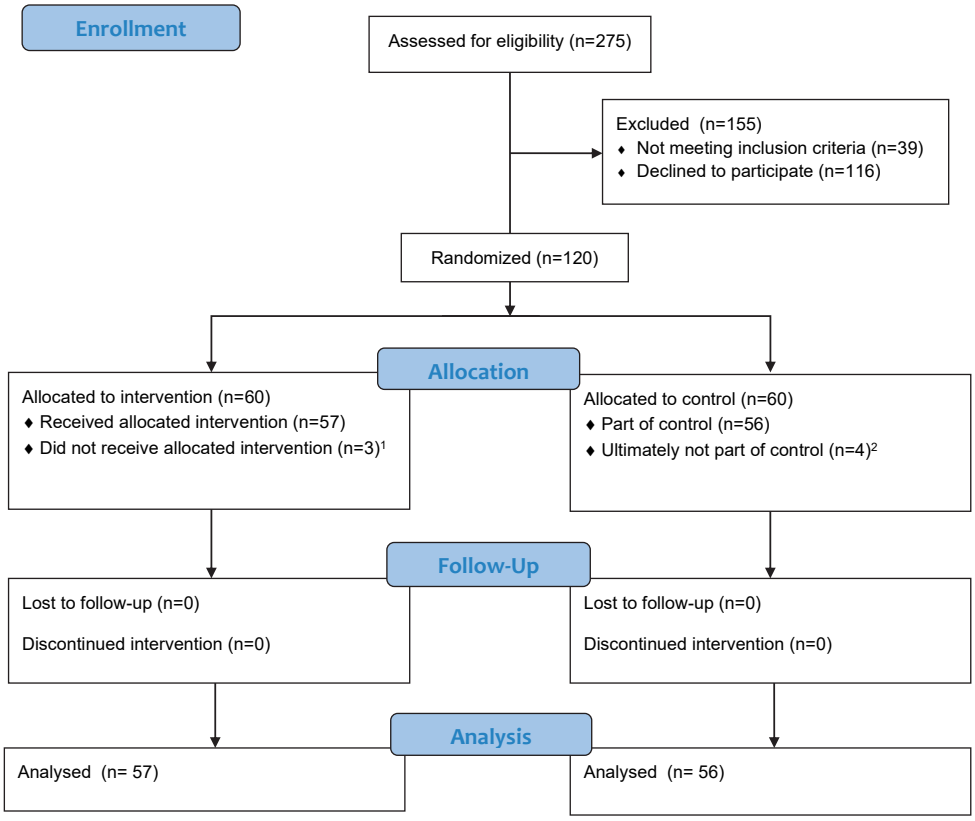

Figure 1. Flowchart of inclusion.

Declined study participation because of previous side-effects with VR interventions(nausea, dizziness, feeling of being seasick), wanting to see the procedure, no additional load by study procedures, no need of VR intervention. [1] Reasons for not receiving the intervention: withdrew consent after giving randomisation results (n=1), thought they also had to sign consent form when they didn't want to participate (n=1), went to another hospital (n=1). [2] Reasons for not being part of the control: withdrew consent after giving randomisation results (n=2), thought they also had to sign consent form when they didn't want to participate (n=1), went to another hospital (n=1).

Table 1. Patient characteristics

Characteristics	Intervention with VR (n=57)	Control without VR (n=56)
Age (year) (mean (SD))	36.18 (3.83)	35.55 (4.05)
BMI (mean (SD))	25.19 (4.37)	23.84 (4.05)
Duration of infertility (years) (mean (SD))	3.70 (2.63)	3.56 (1.56)
Primary infertility (%)	28 (49.1%)	31 (55.4%)
Cause of infertility (%)		
Male infertility	16 (28.1%)	11 (19.6%)
Female infertility	17 (29.8%)	20 (35.7%)
Male and female infertility	5 (8.8%)	5 (8.9%)
Unexplained	19 (33.3%)	20 (35.7%)
Previous fertility treatments [1]		
No previous treatment	13 (22.8%)	14 (25.0%)
Expectant	3 (5.3%)	2 (3.7%)
Intra-Uterine Insemination (IUI)	31 (54.4%)	37 (66.1%)
Ovulation Induction (OI)	2 (3.5%)	4 (7.1%)
In Vitro Fertilization (IVF)	11 (19.3%)	7 (12.5%)
Intra-cytoplasmic Sperm Injection (ICSI)	8 (14.0%)	3 (5.4%)
Type of pain medication used (%)		
Paracetamol	1 (1.8%)	2 (3.6%)
NSAIDs	0 (0.0%)	0 (0.0%)
Opioids (oral)	0 (0.0%)	0 (0.0%)
Anxiolytics	56 (98.2%)	54 (96.4%)
Midazolam	1 (1.8%)	2 (3.6%)
Diazepam	56 (98.2%)	54 (96.4%)
Opioids (IM)	1 (1.8%)	2 (3.6%)
Pethidine		
Morphine		
Dosage of medication used (mean (SD))		
Anxiolytics	7.5 (0.00)	7.5 (0.00)
Midazolam (mg)	10.0 (0.00)	10.00 (0.00)
Diazepam (mg)	137.62 (25.97)	129.17 (22.96)
Opioids (IM)	5.50 (-)	6.75 (0.35)
Pethidine (mg)	1000 (-)	1000 (0.00)
Morphine (mg)		
Paracetamol (mg)		
Number of follicles harvested (mean (SD))[2]	9.05 (6.91)	10.77 (8.37)

[1] Some patients had more than one previous treatment method. [2] Range of duration of the procedure was between 3 and 40 minutes.

Anxiety, pain and patient satisfaction during oocyte retrieval

1. Anxiety experienced by patients undergoing oocyte retrieval

Both participants receiving VR and participants not receiving VR reported 'average perceived stress' according to the STAI grading system. No significant differences were seen between the intervention and control group in pre- and post-procedural anxiety,

measured using the State-Anxiety (STAI-S) (Table 2). Furthermore, no difference was seen in Trait-Anxiety (STAI-T). No significant anxiety reduction in STAI-S and STAI-T, when comparing pre- to post-procedural scores, was seen in either the intervention or control group. The interaction analyses showed no significant influencing factors. No significant correlation was seen between anxiety and overall procedural pain (R=0.010, p=0.305), or between anxiety and worst procedural pain (R=0.03, p=0.08). However, a very weak but statistically significant correlation between post-procedural anxiety and patient satisfaction (R=0.089, p=0.002) was seen (Supplementary figure S1-S3).

Table 2. Difference in anxiety, measured using the State-Anxiety (STAI-S, 'how are you feeling right now') and Trait-Anxiety (STAI-T, 'how are you feeling in general'), calculated between women receiving VR during oocyte retrieval, and women not receiving VR during oocyte retrieval. Anxiety was measured both pre-procedural and post-procedural.

Outcome	Intervention with VR (n=57)	Control without VR (n=56)	Mean difference (95% CI)	P-value [1]
Pre-procedural anxiety (STAI-S) [2] (mean (SD))	43.61 (4.15)	43.75 (5.82)	0.14 (-1.78, 2.05)	0.885
Post-procedural anxiety (STAI-S) [2] (mean (SD))	45.43 (3.89)	45.88 (4.64)	0.45 (-1.21, 2.11)	0.589
Anxiety reduction STAI-S [3] (mean (SD))	-1.75 (5.37)	-1.78 (5.71)	-0.03 (-2.22, 2.15)	0.975
General pre-procedural anxiety (STAI-T) [2] (mean (SD))	45.68 (4.65)	44.92 (3.45)	-0.75 (-2.31, 0.81)	0.340
General post-procedural anxiety (STAI-T) [2] (mean (SD))	45.16 (3.33)	44.78 (3.51)	-0.39 (-1.89, 1.12)	0.611
Anxiety reduction STAI-T [4] (mean (SD))	0.42 (3.57)	0.51 (2.74)	0.09 (-1.34, 1.53)	0.893

[1] Calculated using the independent samples T-test. [2] Score between 20 and 39 is considered 'little perceived stress', a score between 40 and 59 as 'an average amount of stress' and a score between 60 and 80 as 'high perceived stress'.

[3] Calculated by deducting the post-procedural STAI-S score from the pre-procedural STAI-S score.

[4] Calculated by deducting the post-procedural STAI-T score from the pre-procedural STAI-T score.

2. Procedural pain during oocyte retrieval

No significant differences in overall procedural pain, peak pain and time spent thinking about pain were seen between participants receiving VR and participants not receiving VR. When performing an interaction analysis, a near-significant interaction was found between overall pain and the number of follicles punctured (p=0.055). Figure 2 showed that this could be attributed to the difference seen when 10 follicles or fewer were punctured.

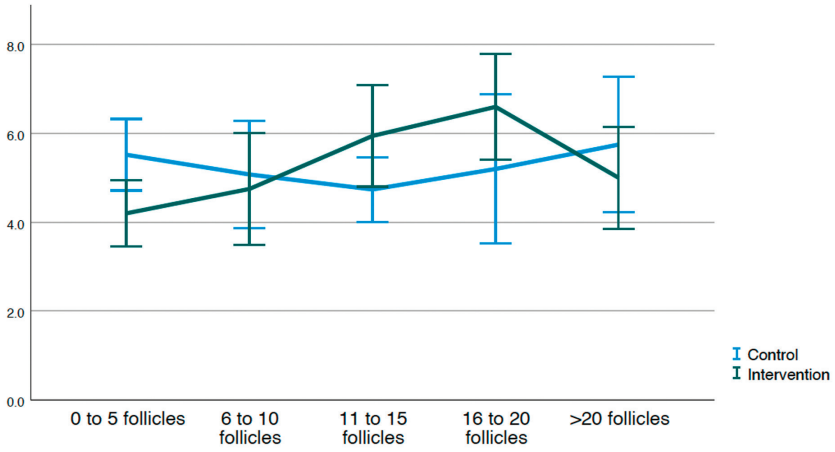

Figure 2. Association between number of follicles harvested during oocyte retrieval and average reported pain scores.

When correcting for the number of follicles (i.e. 10 follicles or less punctured), we saw a significant reduction in overall pain when comparing participants receiving VR to participants not receiving VR (mean difference (MD) 0.93 (95%CI 0.04, 1.83), p=0.041). Age distribution was not different between the two groups (MD 1.02 (95%CI -0.48, 2.52), p=0.181). All other potentially influencing factors (dosage of opioids, age, anxiety scores, VR expectations, duration of the procedure, unilateral or bilateral punction) showed no significant differences.

Table 3. Difference in time spent thinking about pain, in overall and worst pain scores during oocyte retrieval. This was calculated between women receiving VR during oocyte retrieval, and women not receiving VR during oocyte retrieval.

Outcome	Intervention with VR (n=57)	Control without VR (n=56)	Mean difference (95% CI)	P-value[1]
Overall procedural pain (VAS) (mean (SD))	4.00 (1.81)	3.88 (1.39)	-0.12 (-0.97, 0.73)	0.779
Peak procedural pain (VAS) (mean (SD))	5.05 (2.16)	5.64 (2.10)	0.59 (-0.51, 1.68)	0.287
Time spent thinking about pain (mean (SD))[2]	3.21 (1.08)	3.13 (1.08)	-0.08 (-0.49, 0.33)	0.695

Table 3. Difference in time spent thinking about pain, in overall and worst pain scores during oocyte retrieval. This was calculated between women receiving VR during oocyte retrieval, and women not receiving VR during oocyte retrieval. *(continued)*

Outcome	10 follicles or less (n=64)	>10 follicles (n=48)	Mean difference (95% CI)	P-value[1]
Duration of the procedure (min) (mean (SD))	12.72 (7.60)	20.83 (7.79)	-8.11 (-11.02, -5.21)	<0.001
Interactions [3]	**Unstandardized coefficients (B) with 95% CI**			**P-value[3]**
Overall procedural pain scores and number of harvested follicles[4]	-0.08 with 95%CI (-0.17, 0.002)			0.055
Peak procedural pain scores and number of harvested follicles	-0.04 with 95%CI (-0.14, 0.05)			0.378
Outcome [5]	**Intervention with VR (n=37)**	**Control without VR (n=32)**	**Mean difference (95% CI)**	**P-value[1]**
Overall procedural pain (VAS) (mean (SD))	4.41 (1.91)	5.34 (1.80)	0.93 (0.04, 1.83)	0.041

[1] Calculated using the independent samples T-test. [2] Asked on a 5-Point Likert Scale (range 1-5, from "not at all" to "completely/all the time"). [3] Subgroup analyses with interaction between procedural pain scores and number of harvested follicles were studied, calculated using simple linear regression. [4] Difference in overall procedural pain in retrievals where 10 follicles or less were punctured.

3. Procedural patient satisfaction and VR experiences

Procedural satisfaction scores reported by healthcare providers showed no significant differences. Although patient satisfaction scores were high both for participants receiving VR (8.99 (1.04)) and participants not receiving VR (9.34 (0.80)), we did see that participants receiving VR reported significantly lower satisfaction scores (MD 0.35 (95% CI 0.001, 0.702), p=0.050; Table 4). In contrast, participants who underwent oocyte retrieval with VR were significantly less willing to undergo another retrieval without VR (MD 0.86 (95% CI 0.38, 1.33), p<0.001), more willing to undergo another retrieval with VR (MD -1.23 (95% CI -1.61, -0.85), p=0.031) and more likely to recommend VR to others (MD -0.55 (-1.05, -0.06), p<0.001). When performing interaction analyses, we saw that the IVF/ICSI cycle number and VR expectations prior to the procedure did not influence satisfaction scores or the willingness to undergo another retrieval with or without VR. Procedural side effects did not differ significantly among the two groups (Table 4).

Table 4. Procedure satisfaction reported by the patient and healthcare provider, and experienced side effects. Differences were calculated between women receiving VR during oocyte retrieval, and women not receiving VR during oocyte retrieval.

Procedural satisfaction immediately after oocyte retrieval	Intervention with VR (n=57)	Control without VR (n=56)	Mean difference (95% CI)	P-value [1]
Procedural satisfaction score patient[3] (mean (SD)) [2]	8.99 (1.04)	9.34 (0.80)	0.35 (0.001, 0.702)	0.050
Procedural satisfaction score healthcare provider[3] (mean (SD)) [2]	8.46 (1.74)	8.14 (1.44)	-0.32 (-1.03, 0.40)	0.378
Another oocyte retrieval with VR[4] (mean (SD)) 1	4.29 (1.26)	3.74 (1.35)	-1.23 (-1.61, -0.85)	0.031
Another oocyte retrieval without VR[4] (mean (SD)) [1]	3.35 (1.42)	4.21 (1.08)	0.86 (0.38, 1.33)	<0.001
Recommend VR during oocyte retrieval to others[4] (mean (SD)) [1]	4.39 (0.82)	3.16 (1.10)	-0.55 (-1.05, -0.06)	<0.001
Side effects[4] (mean (SD))				
Nausea	1.33 (0.81)	1.24 (0.73)		0.525
Dizziness	1.81 (0.97)	2.10 (1.07)		0.142
Headache	1.11 (0.56)	1.04 (0.19)		0.393
Blurred vision	1.88 (1.15)	2.10 (1.27)		0.345

[1] Calculated using the Pearson Chi-Square test. [2] Calculated using the independent samples T-test. [3] Asked to score their satisfaction on a scale from 1 to 10. [4] Asked on a 5-Point Likert Scale (range 1-5, from "not at all" to "completely/all the time").

The VR experience provided moderate to high distraction (mean 3.55 (SD 0.96) on 5-point Likert scale), and participants experienced moderate immersion in the VR environment (mean 3.11 (SD 1.10) on 5-point Likert scale). A total of 16 participants reported that their expectations were only partially met, with their reasons described in Table 5. Furthermore, reasons for VR removal are described in Table 5.

Table 5. Patient experiences with the VR intervention.

VR experiences	Intervention with VR (n=57)
Headphones worn during the procedure (%)	9 (15.8%)
Pain reduction by VR[3] (mean (SD))	3.30 (1.14)
Distracted by VR[3] (mean (SD))	3.55 (0.96)
Able to concentrate on VR[3] (mean (SD))	3.18 (1.04)
Ability to immerse in VR environment[3] (mean (SD))[1]	3.11 (1.10)
Satisfaction with VR applications[3] (mean (SD))	3.63 (1.00)
VR expectations were met (%)	
Yes	40 (70.2%)
Partially	16 (28.0%)
No	0 (0.0%)
Unknown	1 (1.8%)

Table 5. Patient experiences with the VR intervention. (*continued*)

VR experiences	Intervention with VR (n=57)
Reasons expectations were partially met (%)[2]	
Insufficient distraction	9 (15.8%)
Insufficient pain reduction	1 (1.8%)
Insufficient stress reduction	2 (3.5%)
Confusing to focus on healthcare provider and VR	3 (5.3%)
Blurry images	3 (5.3%)
Technical	2 (3.5%)
Unknown	1 (1.8%)
VR headset removed during the procedure (%)	
Wanting to see what happens	2 (3.5%)
Too much procedural pain	2 (3.5%)
VR headset malfunction	2 (3.5%)
Too sleepy from medication	1 (1.8%)

[1] When performing a confounding analysis, no influence of VR immersiveness was seen by whether the patient wore headphones during the procedure or not. [2] Some women gave more than one reason why VR expectations were only partially met. [3] Asked on a 5-Point Likert Scale (range 1-5, from "not at all" to "completely/all the time").

4. Pain and patient satisfaction 72h after oocyte retrieval

In the first 72h after oocyte retrieval, overall and peak pain scores did not show a significant difference between the intervention and control group. Patient experience of oocyte retrieval was equal in the intervention and control group. With regards to undergoing another oocyte retrieval with and without the VR intervention, as well as recommending them to others, we observed the same results as we did immediately following the procedure. Participants not receiving VR reported significantly more dizziness, headache and blurred vision than participants receiving VR in the first 72h after retrieval (Table 6).

Table 6. Pain scores, procedural satisfaction and experienced side effects 72 hours after oocyte retrieval in IVF/ICSI treatment. Differences were calculated between women receiving VR during oocyte retrieval, and women not receiving VR during oocyte retrieval.

72 hours after oocyte retrieval (mean (SD))	Intervention with VR (n=57)	Control without VR (n=56)	Mean difference (95% CI)	P-value [1]
Overall pain (VAS) (mean (SD))	4.05 (1.83)	4.16 (1.39)	0.11 (-0.67, 0.90)	0.776
Peak pain (VAS) (mean (SD))	5.12 (2.20)	5.77 (2.01)	0.65 (-0.36, 1.66)	0.201
Procedural satisfaction [2]	Intervention with VR (n=57)	Control without VR (n=56)	Mean difference (95% CI)	P-value [1]
Experience of oocyte retrieval (mean (SD))	3.50 (0.90)	3.42 (0.95)	-0.08 (-0.48, 0.32)	0.694
Another oocyte retrieval with VR (mean (SD))	4.35 (0.96)	3.42 (1.24)	0.97 (0.53, 1.40)	<0.001
Another oocyte retrieval without VR (mean (SD))	3.38 (1.08)	4.34 (0.91)	-0.93 (-1.42, -0.45)	<0.001

Table 6. Pain scores, procedural satisfaction and experienced side effects 72 hours after oocyte retrieval in IVF/ICSI treatment. Differences were calculated between women receiving VR during oocyte retrieval, and women not receiving VR during oocyte retrieval. (*continued*)

72 hours after oocyte retrieval (mean (SD))	Intervention with VR (n=57)	Control without VR (n=56)	Mean difference (95% CI)	P-value [1]
Recommend VR during oocyte retrieval to others (mean (SD))	4.35 (0.76)	3.08 (0.88)	-1.28 (-1.63, -0.92)	<0.001
Side effects (mean (SD))				
Nausea	1.54 (0.97)	1.76 (1.13)		0.065
Dizziness	1.60 (0.87)	2.05 (0.93)		0.044
Headache	1.42 (0.68)	1.61 (1.03)		0.047
Blurred vision	1.33 (0.60)	1.87 (1.04)		0.033
Tiredness	3.08 (1.05)	3.53 (1.06)		0.303
Concentration problems	2.04 (0.97)	2.61 (1.18)		0.112

[1] Calculated using the Pearson Chi-Square test. [2] Questions were asked on a 5-Point Likert Scale (range 1-5, from "not at all" to completely/all the time").

DISCUSSION

This is the first study investigating the effect of VR on anxiety and pain during oocyte retrieval. We found no significant differences in anxiety, overall and peak pain between participants receiving VR and participants not receiving VR. We found no significant anxiety reduction when comparing pre- to post-procedural scores. Participants receiving VR reported significantly lower procedure satisfaction scores immediately after oocyte retrieval but were significantly more inclined to undergo another retrieval with VR and more likely to recommend VR during retrieval to others.

Previous studies on the use of VR during gynaecological procedures are contradictory. Where some found no effect of VR on anxiety, pain and patient satisfaction during HSG and colposcopy, others did find it effective in similar gynaecological procedures like hysteroscopy, HSG, amniocentesis and episiotomy repair [26-28,30,31,34-36]. Additionally, strong correlations between anxiety and pain have been suggested. Severe anxiety was associated with an increased demand for pain medication and pre-operative anxiety has been found a predictor of postoperative pain in hysterectomy patients [15,32]. In our study we primarily provided VR during the procedure, which could explain why we found no effect on anxiety and pain. Since VR was only shortly provided during the waiting time, with the aim of trying out the intervention rather than reducing pre-procedural anxiety, it might have been suboptimal in reducing pre-procedural anxiety and thereby procedural pain. For future studies, the effect of VR on pre-procedural anxiety and consequently on post-procedural pain should be further investigated.

In addition, VR might only be effective up to a certain pain threshold but when pain exceeds this threshold or the procedure takes longer, pain management might become insufficient. Van Barneveld et al. (2023) found that the reporting of overall pain scores was influenced by recall bias when patients were asked to retrospectively score their pain. It resulted in them overestimating pain intensity [37]. In our study, it might be that the oocyte retrieval was manageable in terms of pain at first, but intensified after a certain time, making distraction of the VR intervention and its effect on pain no longer sufficient. Therefore, participants might have scored based on this more intense pain, already forgetting the manageable pain at the start of the procedure, leading to a possible overestimation. In our interaction analysis, we found significantly lower overall pain scores in the intervention group when 10 follicles or less were punctured. These retrievals were found significantly less time-consuming and less aspiration attempts were often needed to collect all follicles. This could suggest that small retrievals are associated with less pain, but it might also be that overall pain scores were less affected by recall bias as the duration of the procedure was significantly shorter. Nevertheless, since we did not base our sample size on this finding, we cannot attribute this effect on pain scores to VR with full certainty.

VR has been proven to be a safe treatment method with minor and short-term side effects. In our study, we found that participants in the intervention group experienced less side effects such as dizziness, headache, and blurred vision in the first 72h after retrieval, compared to participants in the control group. This might be due to the fact that VR has been proven successful as vestibular rehabilitation (a therapy to manage dizziness, headaches and balance issues) in case of vertigo [38]. Nonetheless, despite generally high patient satisfaction, participants in the intervention group reported significantly lower satisfaction scores. This could be partly explained by technical difficulties with the VR intervention at times, but it is also possible that it resulted from unmet expectations of VR. Participants whose expectations were only partially met, attributed this to the fact that VR provided them insufficient distraction, or pain or anxiety reduction. Interestingly however, participants receiving VR were significant more willing to undergo another retrieval with VR, and less willing to undergo another retrieval without VR. It is possible that, although the VR intervention has not been proven optimally effective, participants still experienced a sense of control regarding their anxiety and pain management. Previous studies found that improved self-management skills had a positive effect on quality of life and patient satisfaction, in patients diagnosed with chronic disorders [39-41]. This is similar to findings in our previous study, where we applied VR during HSG. We found no effect on overall and peak pain scores, but did find that patients receiving VR during HSG were significant more willing to undergo another HSG with VR, and less willing to undergo another HSG without it [34]. It might therefore be that although VR objectively did not provide anxiety and pain relief and the participants' expectations were not always fully met, they might still have perceived VR as a valuable tool to offer some level of distraction or comfort, making them prefer it in future procedures. Furthermore, it might have

offered participants a sense of control or provided an additional coping mechanism. This might have made them feel more empowered or better equipped to handle the procedure, leading to more willingness to undergo the procedure again with VR despite lower satisfaction. Patient satisfaction is considered important, as studies linked it to better medication adherence, better treatment outcomes, lower healthcare costs, and improved health-related quality of life [42-44]. There is a growing recognition that innovations in treatment should focus on more than just pain relief, and healthcare providers emphasize the importance of adopting a holistic approach. This approach addresses a spectrum of health domains and assesses patients' unmet needs at baseline while tracking treatment-induced improvements across these domains [45]. As a result, patient satisfaction could be considered an important outcome measure, potentially outweighing pain and/or anxiety reduction.

In future studies, it might be interesting to investigate whether VR could be further tailored as generic VR interventions might not achieve the optimal desired effect. Not all patients might react similarly, and might want to gain different things from the VR intervention or might need different stimuli in order to achieve optimal anxiety and pain management, making it interesting to add patient preferences when developing new VR software. Pardini et al. performed a pilot study and found that a personalized VR intervention was more effective in reducing patient reported anxiety and tension, compared to a standard VR intervention. They stated that further research was needed [46]. In addition, it could be interesting to include which subgroup of patients will benefit from a VR intervention and when they will benefit most. It is possible that patients of older age might respond differently to the VR intervention than those of younger age, where the VR devices could be more effective in optimizing positive emotions in younger patients [47]. Nevertheless, in our study, we saw no significant differences in age distribution between our groups and age itself was no influencing factor. However, the interaction analysis did suggest that participants undergoing smaller and quicker retrievals benefitted more from the VR intervention, which might suggest that VR is most effective when applied during shorter gynaecological procedures with lower baseline pain scores. Furthermore, it is also possible that VR is more effective in reducing pre-procedural anxiety and thereby influence procedural pain. Finally, it can be questioned whether the infertile patient is the right patient to provide VR to. They have already had to change their expectations and have experienced a loss of control over when and how they become pregnant, but do have control over how they undergo oocyte retrieval. The fact that about 50% of eligible patients declined study participation, with the most frequent reason being that they wanted to see what happened, keep control and/or wanted to keep in contact with the healthcare provider, could also be an indication of this (Supplementary Table S1). Some patients who declined participation mentioned that they felt the retrieval was the closest they came to conceiving a child together, making that they wanted to be present during the procedure. Therefore, it is important to further explore patient preferences by in-

depth interviews or analysing qualitative feedback, to understand their views on anxiety and pain management during IVF/ICSI treatment.

Strengths and limitations

Our study has several strengths. First, we added sound to the VR environment to optimize VR immersiveness, an important factor in reducing pain and/or anxiety [48]. Also, because in our previous study where VR was provided during HSG, we saw that adding sound might improve the efficacy of VR and participants reported missing sound from the VR intervention with a mean score of 2.5 (SD 1.30), on a 5-point Likert scale [34]. Furthermore, all eligible patients were counselled by the same researcher to ensure consistency of information. Finally, we performed interaction analyses to explore whether VR was more effective for certain patient groups. Our study also has several limitations. First, a significant number of patients declined to participate in the study (112/232), with frequently mentioned reasons that participants wanted to see and hear what was happening. This could have introduced selection bias. In addition, healthcare providers had to communicate with the patient at times, potentially leading to reduced VR immersiveness. Furthermore, all participants received conscious sedation, which might have contributed to suboptimal VR immersiveness. Since they were somewhat dazed from medication, they might have been unable to focus on the VR intervention optimally. However, no studies support this statement, and with the exception of one participant, we often saw that patients were very alert. In addition, the VR intervention was not tailored to the procedure or the specific patient preferences, although patients were able to choose which nature film or relaxation exercise was most appealing to them. Therefore, the generic VR intervention might not have achieved optimal pain and anxiety management. However, at the time of initiation of our study, personalization of the VR intervention was not available. Additionally, since both the participant and researcher dedicated to the trial were not blinded, this might have contributed to performance bias. Furthermore, a total of seven participants removed the VR headset, with reasons described in Table 5. Finally, we did not objectify anxiety after the VR intervention was provided in the waiting time prior to the procedure. It might be that VR is more effective in reducing pre-procedural anxiety and thereby procedural pain. This should be further assessed in future studies.

CONCLUSION

We did not find an effect of VR on anxiety and procedural pain. However, the interaction analysis suggested VR might be effective in reducing overall pain for participants undergoing a retrieval where 10 of fewer follicles were punctured. However, since we did not base our sample size on this finding, we cannot attribute this to VR with full certainty. Nonetheless, it might suggest that VR only reduces pain up to a certain threshold and for a certain period of time, but is no longer effective when it exceeds this. Furthermore,

it is important to investigate which subgroup could benefit from VR and would want to implement this in their anxiety and pain management. Therefore, patient preferences are an important outcome measure and patient views on anxiety and pain management during IVF/ICSI treatment should be explored. The infertile patient might not be the right patient to provide VR to. We saw that there was a great need for control during the puncture among patients. In conclusion, based on the results of this study, we do not advise incorporating VR during oocyte retrieval in standard IVF/ICSI anxiety and pain management.

QR code to article for supplementary materials



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Part II

Standardizing pain management and the appliance of Spinal Cord Stimulation in endometriosis





Chapter 5

Standardizing pain management for the endometriosis patient: a Dutch modified Delphi procedure

Annelotte van Haaps, Anneke Schreurs, Robert de Leeuw, Jan Willem Kallewaard, Misha Erwteman, Judith Dekker, Ingeborg Melgers, Eric van der Horst, Jakko Nieuwenhuizen, Kristien Tytgat, David Heineman, Kim Dreyer, Velja Mijatovic

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ABSTRACT

Objective: to develop a step-by-step guideline to the medical management of pain in women with endometriosis from a national modified eDELPHI process in the Netherlands.

Methods: an eDELPHI procedure was preceded by an multidisciplinary expert meeting with experts in Obstetrics and Gynaecology (OBGYN), Colorectal Surgery, Anesthesiology, Urology, and Gastro-Enterology to develop a flow diagram for endometriosis pain management. The flow diagram was tested in two rounds of an eDELPHI procedure among experts in the field of OBGYN and Anesthesiology. They were recruited through a digital newsletter. For each item, it was predefined that consensus would be reached when at least 70% of respondents agreed.

Results: consensus was reached on all but one item. The first two steps adhere to the WHO step-by-step approach. The third step in endometriosis management is the addition of TCAs in case of neuropathic pain. It is recommended only to use metamizol and opioids for the short term. Muscarinic receptor antagonists are accepted treatment for bladder endometriosis. The use of COX-2 inhibitors is suggested but is not an established step in pain management. It is advised to prescribe magnesium hydroxide with all types of pain management because of its positive effect on gastro-intestinal symptoms. Finally, proton pump inhibitors (PPIs) can be prescribed with use of NSAIDs.

Conclusions: consensus on a step-by-step guideline on pain management between Dutch endometriosis care experts was achieved. However, the use of some medication types are based on limited scientific evidence, underlining the importance to further investigate pain management options for endometriosis.

Highlights

- A modified eDELPHI procedure among Dutch endometriosis experts created a flowchart for medical pain management.
- Step 1 and 2 of the step-by-step WHO pain approach remain, with TCAs added as a third step for neuropathic pain.
- Experts agreed opioids should only be used for acute pain, for example after surgery, not for chronic endometriosis pain.
- Consensus was reached on using muscarinic receptor antagonists in bladder endometriosis.
- COX-2 inhibitors were considered promising but not included as a step in the flowchart due to limited evidence.

INTRODUCTION

Endometriosis is a chronic, estrogen-dependent inflammatory disease and defined as the presence of endometrium-like tissue outside the uterus [1]. Approximately 190 million women are affected worldwide [1,2]. The classic triad of endometriosis-associated symptoms include dysmenorrhea, deep dyspareunia and chronic pelvic pain. Other symptoms include dysuria, dyschezia and infertility but also gastro-intestinal symptoms like bloating and abdominal cramping [1,3,4]. Traditionally, the concept of (chronic) pain is explained through a linear relationship between identifiable organic pathology and patient-reported symptoms [5]. However, the extent of disease does not always correspond with pain intensity experienced by patients. Women with mild stage endometriosis may be highly symptomatic, while others with severe stage endometriosis can be asymptomatic [6-8]. Recently, perspectives on chronic pain increasingly draw on the biopsychosocial model which conceptualizes pain and its related disability as the result of a multidimensional, dynamic interaction between physical, psychological and social factors, each affecting one another [5]. Severe symptoms can result in psychological diagnoses such as depression and anxiety whereas the presence of these conditions can be an important risk factor for the transition from acute to chronic pain. Therefore, it is important to assess, diagnose, and consequently treat chronic pain from a broad perspective that includes multiple social and psychosocial factors, rather than focusing solely on physical factors.

Since endometriosis is chronic and currently not curable, endometriosis treatment mostly consists of managing symptoms and is based on three pillars: hormonal therapy, surgery and pain management [1]. Although pain management does not directly suppress endometriosis lesions, it can have an anti-inflammatory effect by inhibiting the release of pain neurotransmitters [9]. Physicians mostly adhere to the WHO step-by-step approach for pain management [9]. However, this approach was initially developed for cancer patients, and might therefore not be suitable for endometriosis patients as their pain mechanisms can differ [10]. As a first step in treatment, patients are advised to buy over-the-counter medication such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Although multiple studies found NSAIDs very effective in reducing dysmenorrhea in general, their use for endometriosis-related symptoms is based on one, low-quality study [1]. Caution in use is needed because overdosing and side effects are associated with its use [9,11,12]. Opioids are part of the third step on the WHO step-by-step approach. However, they do not seem very effective in reducing chronic endometriosis-related pain and might only be effective in reducing acute inflammatory pain. Because of their highly addictive character, caution should be applied when prescribing them for an incurable, chronic disorder [9]. Alternatively, in patients with persistent chronic pain, neuromodulators like selective serotonin uptake inhibitors (SSRI's), anti-depressants or anti-convulsants can be prescribed [1]. They primarily affect central nervous system pain modulation rather than peripheral meditators of inflammation and have shown promising effects in reducing

endometriosis-related pain. However, superiority over placebo has not been proven clearly and they can cause severe, dose-limiting side effects [1,13].

Currently there are no clear step-by-step guidelines on medical pain management for endometriosis patients and pain management can differ between patients and healthcare providers. Therefore, the aim of this study is to provide a multidisciplinary expert consensus and create a step-by-step guideline for medical pain management in endometriosis. The many non-medical ways to treat pain fall outside of the scope of this study [14].

METHODS

We conducted a modified eDELPHI process to develop national consensus on step-by-step medical endometriosis pain management in the Netherlands. We chose to perform a modified eDELPHI procedure to create a knowledge basis for an international eDELPHI procedure. Ultimately, we aim to reach international consensus on medical pain management for endometriosis in future research. The institutional review board of Amsterdam University Medical Center, location Academic Medical Center has approved this study (2023.0561).

Expert consensus meeting

The Dutch modified eDELPHI procedure was preceded by a multidisciplinary consensus meeting, held between experts from the Amsterdam University Medical Center (AUMC). Experts were affiliated to the AUMC Endometriosis Center, a Dutch Level-2 endometriosis expertise center and tertiary referral center [15]. They work in the field of Obstetrics and Gynaecology (OBGYN), Cardiothoracic Surgery, Anesthesiology, Urology and Gastro-Enterology. They provide care to endometriosis patients from their area of expertise and are all long-term members of the AUMC multidisciplinary endometriosis team. All experts provided informed consent before participating in the consensus meeting and attended in person or digitally. The meeting was moderated by a trained and experienced independent moderator (AS). A set of pre-defined questions was designed to guide the development of a flow diagram for medical endometriosis pain management. During the consensus meeting, experts were asked to write down all pain management options they used in their field of expertise when treating endometriosis patients. The independent moderator collected the treatment options and further discussed them with the group of experts. The pre-defined regulatory questions were as follows:

- The importance of the discussed medical pain management option within endometriosis treatment;
- The observed effects, patient experiences;
- Considerations when applying the specific treatment method;

- Potential side effects or drawbacks and the degree of agreement among other healthcare professionals regarding its place in standard care.

Responses were collected across iterative rounds to identify consensus and refine priorities. We included accompanying steps, such as adding proton pump inhibitors (PPI) or laxatives. At the end of the meeting, a first draft of a flow diagram for medical endometriosis pain management was prepared. Afterwards, the researcher further developed the diagram and distributed it by email to the experts who had attended the consensus meeting. Their comments were incorporated in the flow diagram, resulting in a flow diagram on medical endometriosis pain management that could be tested in an eDELPHI procedure.

Electronic DELPHI procedure

An eDELPHI is a multistage process in which consensus among experts is reached through a series of structured questionnaires. The number of rounds in which a structured questionnaire is distributed is dependent on how quickly consensus among the experts is reached. In each round, experts can indicate if they disagreed with the question, and mention reason(s) why. These answers are processed in the structured questionnaire for the next round. In this study, we considered consensus reached when the rate of agreement (RoA) was >70%. This was calculated using the equation: $RoA = (agreement - disagreement) / (agreement + disagreement + neutral) \times 100\%$ [16]. Questions were rephrased and resubmitted in the next round when the RoA was less than 70%. After the eDELPHI rounds, a consensus meeting was held among the study's researchers to discuss the items on which no consensus was reached.

In this Dutch modified eDELPHI procedure, we distributed the flow diagram on medical endometriosis pain management among experts from the Departments of OBGYN and the Departments of Anesthesiology. They were recruited through a digital newsletter from the Dutch association for gynecologists and the Dutch association for anesthesiologists. We considered healthcare providers experts in endometriosis care if they had at least five years of experience in the field and consulted at least ten endometriosis patients each year. All participants provided informed consent before being able to enter the eDELPHI procedure.

RESULTS

Multidisciplinary expert consensus meeting

A consensus meeting preceded the eDELPHI among experts affiliated to the Endometriosis Center of the Amsterdam UMC. Ten experts attended the meeting of which five worked at the Department of OBGYN, one at the Department of Anesthesiology, two at

the Department of Urology, one at the Department of Cardiothoracic Surgery, and one at the Department of Gastro-Enterology. During this meeting, a first version of a flowchart was drawn up on medical pain management for the endometriosis patient. This flowchart was tested in the eDELPHI procedure and is shown in Appendix Figure 1.

Experts agreed that step 1 and step 2 of the WHO step-by-step approach should remain unchanged. As a consequent step, they proposed replacing NSAIDs with Cyclo-Oxygenase-2 (COX-2) inhibitors because of their overlap with opioids without a gastro-intestinal effect. Although not frequently prescribed, they were considered very effective. Metamizol, part of the NSAIDs group and an effective painkiller and spasmolytic, is not frequently prescribed in the Netherlands and not reimbursed by Dutch insurance [17]. The experts recommended limiting their use due to the severe side effects of agranulocytosis. As a third step, tricyclic anti-depressants (TCAs) like amitriptylin or pregabalin for neuropathic pain early in the sequence of medical pain management options were suggested. Experts agreed that opioids (oxycodone, oxynorm, tramadol) should only be applied as acute medical pain management for example during withdraw bleeding or for post-operative pain. Caution is implied due to their highly addictive character, patients should be thoroughly counseled, and it should be emphasized that no repeat prescription will be given. Experts from the department of OBGYN preferred tramadol drops because they allow people to add small dosages (less than 50 mg each time). Although outside the scope of this study, complementary pain management options such as Transcutaneous Electric Neurostimulation (TENS), CBD oil that only has an analgesic effect since it does not contain tetrahydrocannabinol (THC), and self-management strategies were also debated and presented in the flow diagram. The expert from the Department of Gastro-Enterology recommended prescribing PPI's with all NSAID use because the risk of gastro-intestinal symptoms also increases with short-term NSAID use [18].

They also advised the use of laxatives with all pain medication. The sequence of laxatives is based on chronic pain management for cancer patients, in which osmotic (e.g. macrogol) or stimulant (e.g. bisacodyl, sodium picosulfate) laxatives are given first [19]. Since osmotic laxatives have fluid-attracting properties that can increase volume load and thereby potentially increase visceral pain, the experts participating in the consensus meeting preferred stimulant laxatives as the first option. Magnesium hydroxide can have a relaxing effect on skeletal and intestinal smooth muscles, thereby alleviating gastro-intestinal symptoms associated with endometriosis [3,20]. Caution with chronic use is implied since long-term relaxation of smooth muscles can result in the same set of symptoms that it was provided for to alleviate [20].

Electronic DELPHI procedure

Between April 2024 and February 2025, two rounds of an electronic DELPHI (eDELPHI) were performed. In the first round a total of 37 experts responded. Only 20 respondents

met the inclusion criteria and where presented with the eDELPHI questions. All respondents of round one were sent the second round of the eDELPHI procedure. Of the 20 respondents who completed the questions in the first round, a total of 13 respondents completed the second round (Table 1).

Table 1. Baseline characteristics of eDELPHI respondents and participants.

	Round 1 (N=37)		Round 2 (N=13)
	Total number of respondents	Meeting inclusion criteria	
Field of expertise (%)			
Gynaecologist	20 (54.1%)[1]	18 (48.6%)	12 (92.3%)
Anesthesiologist	17 (45.9%)[1]	2 (5.4%)	1 (7.7%)
Hospital (%)			
Secondary center	23 (62.2%)	11 (29.7%)	8 (61.5%)
Tertiary center	14 (37.8%)	9 (24.3%)	5 (38.5%)

[1] Exclusion because less than 10 endometriosis patients consulted them each year (n=2), because they worked less than 5 years in the field of endometriosis (n=5), or both (n=10).

eDELPHI round 1

It was aimed to reach consensus on the definition of endometriosis-related pain, bladder endometriosis, chronic use of medication and neuropathic pain. Not to rephrase its definitions, but to ensure all experts had a common understanding. Both the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) give no clear definition of endometriosis-related pain. In an opinion piece, the ASRM defines endometriosis-related pain as follows (direct quote): "*pain resulting from production of substances such as growth factors and cytokines by activated macrophages and other cells associated with functioning endometriotic implants, the direct and indirect effects of active bleeding from endometriotic implants; and irritation of pelvic floor nerves or direct invasion of those nerves by infiltrating endometriotic implants, especially in the cul-de-sac*" [21]. However, only 30% of our experts agreed with this definition. All experts agreed on the definition from Maddern et al.(direct quote): "*Visceral and somatic pain caused by inflammation of peritoneal liquid and endometriosis lesions, neurogenic inflammation, central and peripheral sensitization*" [22]. Nonetheless, in the open-ended questions experts stated that this definition missed the multidimensional and chronic aspects of endometriosis, the involvement of central and peripheral sensitization, and the distinction between superficial and deep endometriosis. Experts agreed both on the diagnosis of bladder endometriosis and the definition of chronic use of pain medication in the first round [Table 2] [23].

Table 2. Definitions per topic, consensus outcomes, and summary of open-ended feedback from eDELPHI participants in round 1. Consensus was defined as ≥70% agreement.

Item	Chosen definition	Decision	Open-ended answers
Definition of endometriosis-related pain Maddern et al. "*Visceral and somatic pain caused by inflammation of peritoneal liquid and endometriosis lesions, neurogenic inflammation, central and peripheral sensitization".* ASRM 2014. "*Pain resulting from production of substances such as growth factors and cytokines by activated macrophages and other cells associated with functioning endometriotic implants, the direct and indirect effects of active bleeding from endometriotic implants; and irritation of pelvic floor nerves or direct invasion of those nerves by infiltrating endometriotic implants, especially in the cul-de-sac*"	14 (70%) 6 (30%)	Consensus	- Multidimensional aspect underexposed. - No distinction between deep and superficial endometriosis. - Chronic aspect is missing. - Central and peripheral sensitization is not mentioned. - Pelvic floor hypertonia is not mentioned.
Definition of neuropathic pain Treede et al. "*Pain that arises as a direct result of a lesion or disease affecting the somatosensory nervous system. This includes both the nociceptive system, the ascending and descending pathways.*" IASP. *"Neuropathic pain is defined as pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system"*	7 (35%) 13 (65%)	No consensus	- Term nociceptive is not included.
Bladder endometriosis Presence of symptoms related to bladder endometriosis Presence of lesions on imaging, in addition to symptoms	3 (15%) 17 (85%)	Consensus	- Based on whether at least serosal bladder involvement is seen on imaging.
Chronic use of medication Guideline polypharmacy. "*Use of medication ≥90 days per year, or >3 prescriptions in the past year".* Von Korff et al. "*Use of medication for at least 2 months, on a daily basis".*	17 (85%) 3 (15%)	Consensus	- Both definitions incomplete. For example when people switch medication which are still from the same group. - >90 consecutive days, not use for 90 out of 365 days. On the other hand; if someone takes painkillers every month in her cycle for e.g. 3 days it would still be labeled chronic use. - >3 prescriptions is vague, since paracetamol and NSAIDs are not prescription drugs. Also dependent on the number of tablets per prescription. 4 times 10 tablets of morphine I'd not define as chronic use.

No consensus was reached on the definition of neuropathic pain in the first round of the eDELPHI procedure, where the definition of the International Association for the Study of Pain (IASP) was used (direct quote): "*neuropathic pain is defined as pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system*" [24]. In the open-ended questions, our experts mentioned they missed certain aspects from the definition, mainly that the term 'nociceptive' was not included. Although it was not intended to redefine either definition, the fact that experts did not agree on both in the first round of the eDELPHI procedure could suggest a need for redefinition. Details of all answers to the open-ended questions are in Table 2.

Next, the flow diagram was tested with 23 questions. In the first round, consensus was reached on the steps involving the use of paracetamol, NSAIDs and TCAs in standard medical pain management. Experts agreed that opioid use was only fitting when applied as acute pain management. The fact that some medication was expensive and not reimbursed by health insurance were reasons experts did not prescribe them. More than 70% of experts stated that they considered the use of PPIs only needed in case of chronic use of NSAIDs [23] and use of laxatives when prescribing opioids or muscarinic receptor antagonists. In the first round, no consensus was reached on the switch of NSAIDs to COX-2 inhibitors and on the use of muscarinic receptor antagonists in case of bladder endometriosis [Table 3].

Table 3. Questions on the flow diagram, the consensus outcomes, and summary of open-ended feedback from eDELPHI participants in round 1. Consensus was defined as ≥70% agreement.

Item	Answer "Yes"	Decision	Open-ended answers
Step 1. Paracetamol	18 (90%)	Consensus	- In case of dysmenorrhea only, just NSAIDs can be considered due to its better working mechanism.
Step 2. NSAIDs	19 (95%)	Consensus	
Preference Ibuprofen Preference Naproxen No preference	2 13 5	Consensus	
Added PPI to step 2	15 (75%)	Consensus	
Also when incidental NSAIDs use[1] Only when chronic NSAID use	2 (13.3%) 13 (86.7%)	Consensus	
Step 3. Switch NSAIDs to COX-2 inhibitors	7 (41.2%)	No consensus	- Can be questioned whether it helps - Can be administered immediately. - No added value of a COX-2 inhibitor. - No experience with its use, not used to prescribe it. - Not in my arsenal right now. When combination paracetamol/NSAIDs is insufficient I switch to alternatives like TCA or tramadol/oxycodone.
Step 4. TCAs in case of neuropathic pain	14 (77.8%)	Consensus	- Preferred to first start NSAIDs after paracetamol before adding TCAs.
Prescribe laxatives	19 (95%)	Consensus	
Only added to opioids or muscarine receptor antagonists Always, in any type of pain medication Only in case of gastro-intestinal symptoms	1 (5%) 14 (70%) 5 (25%)	Consensus	- Only when gastro-intestinal problems. - Not with paracetamol of NSAIDs alone. Too much medication. - Only with opiates. - Would like to have the evidence to prescribe laxatives standardly. - Is it cost-effective to prescribe this as a standard? Financial burden for healthcare - Depending on age, medical history, symptoms etc. - Only when indicated. - Has to be taken for a couple of days or times for it to be effective.

Table 3. Questions on the flow diagram, the consensus outcomes, and summary of open-ended feedback from eDELPHI participants in round 1. Consensus was defined as ≥70% agreement. (*continued*)

Item	Answer "Yes"	Decision	Open-ended answers
Tramadol, opioids or metamizol only in case of acute pain	16 (80%)	Consensus	
Opioids are also part of chronic pain management for endometriosis Opioids can only be used short-term (post-operative or during menstruation) Opioids are no part of pain management For endometriosis	3 (15%) 16 (80%) 1 (5%)	Consensus	- Too brief. Use depends on the patient, endometriosis, remediation surgery. Was there multidimensional evaluation? Are they already suppressed using hormones? Only weak opiates and metamizol are indicated; no strong opiates. - Tramadol drops as preferred option because it's easier to titrate. - Take the effect on participating in traffic, at work into account. - Metamizol use only clinically, no use at home and switch at hospital discharge. There are better alternatives. - Restraint with opioids use due to its addictive character. - Restraint with opioids due to its gastro-intestinal effects.
High costs and no reimbursements are reasons not to prescribe medication	15 (75%)	Consensus	
Muscarine receptor antagonists in case of bladder endometriosis[3]	12 (66.7%)	No consensus	
Short term as abridgement towards operation Long term use	6 (100%) 0 (0%)	Consensus	- Start with regular pain management and expand based on effect - No experience with its use. - Only when symptoms can only be explained by presence of bladder endometriosis. Low threshold consultation with urologist. - Provided there are complaints of urgency.
Advise alternative pain management options to manage endometriosis-related pain	15 (75%)	Consensus	- Not evidence based. - I never advise CBD oil. - Get this step to the front. And then also add movement and sleep education.

[1] Of the 15 people who added PPIs to NSAID use. [2] Consensus on the fact that they did not add laxatives to all types of pain medication.[3] Consensus on the fact that they did not prescribe muscarine receptor antagonists in case of bladder endometriosis

The answers to all open-ended questions were used to rephrase the questions and distribute them among the experts in a second eDELPHI round. The questions of the first eDELPHI round can be found in Appendix 1.

eDELPHI round 2

Results of the second round are displayed in Table 4. First, the definition of neuropathic pain was adjusted whereafter consensus was reached [Table 4]. In the second round, literature was added to further substantiate the use of muscarinic receptor antagonists in medical endometriosis pain management, after which consensus was reached. However, after adding substantiating literature on the use of COX-2 inhibitors in medical endometriosis pain management, consensus was still not reached. Therefore, its use was discussed in a researchers' consensus meeting [25].

In the 2022 EHSRE guidelines, no specific mention is made on the use of COX-2 inhibitors for endometriosis-related medical pain management [26]. Cobellis et al. [27] studied the effect of COX-2 inhibitors on pain symptoms, where they compared Rofecoxib to placebo in 28 endometriosis patients who had first undergone conservative surgery for symptomatic endometriosis. They found significant improvement of chronic pelvic pain and dyspareunia after six months. They stated that larger studies should be performed to substantiate their results [27]. More recently, Park et al. analyzed 33,406 patients over a period of 28 years, finding that COX-2 inhibitor use was associated with a lower incidence of endometriosis than NSAID use, especially in women aged 20-44 years. This could suggest that COX-2 inhibition not only reduces symptoms but also reduces disease progression by suppressing PGE2, ultimately inhibiting lesion growth [28]. Finally, it was decided to present the use of COX-2 inhibitors as a suggested option rather than a fixed one, as further research on their application in medical endometriosis pain management is needed. After two rounds of the eDELPHI procedure the a final flow diagram was developed [Fig. 1]. All questions of the second eDELPHI round can be found in Appendix 2.

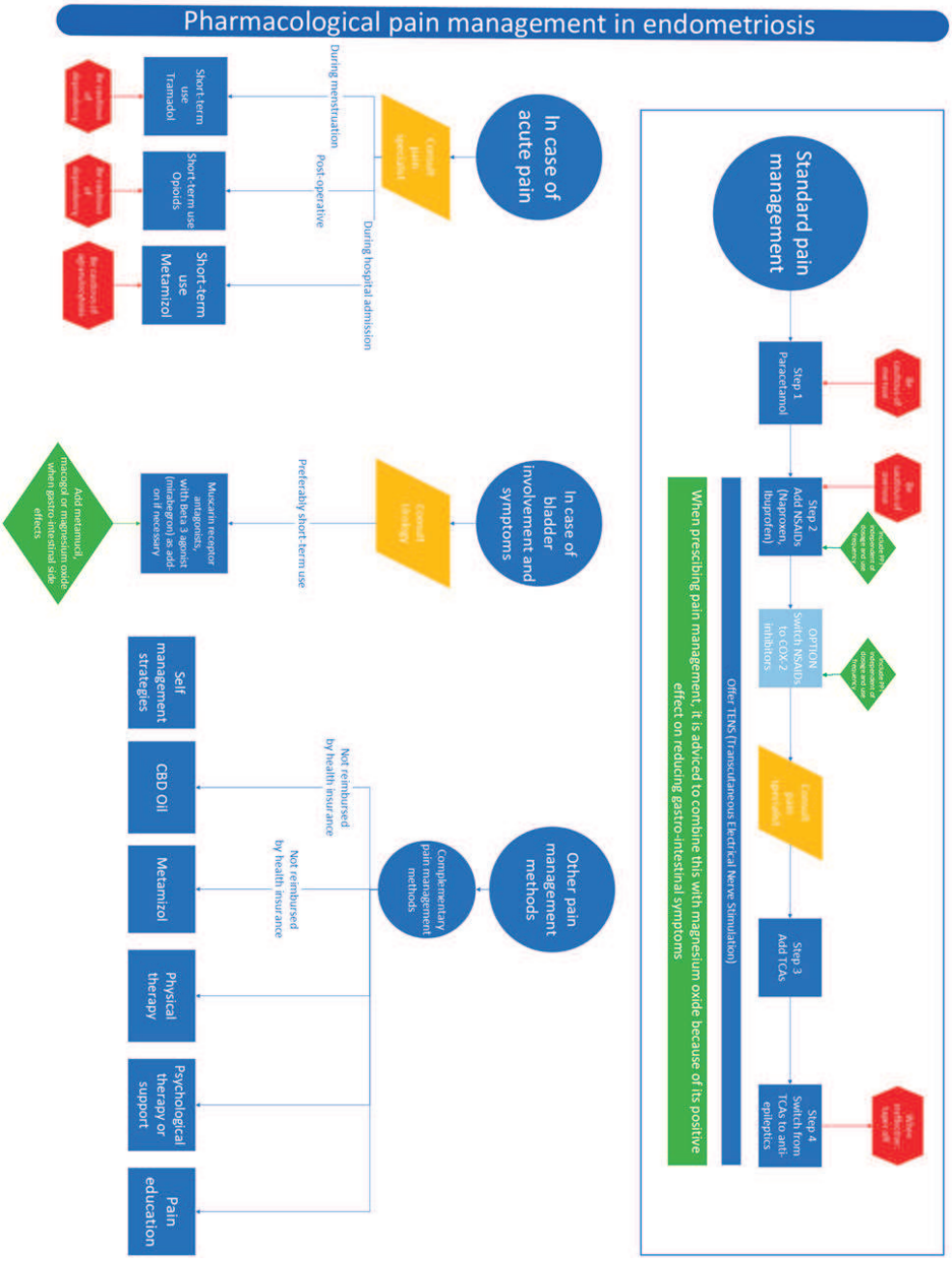

Figure 1. Definitive flowchart of pain management in endometriosis patients, deducted by the expert consensus meeting followed by two rounds of an eDELPHI procedure.

DISCUSSION

To the best of our knowledge, this is the first study to develop a flow diagram for medical pain management in endometriosis using an eDELPHI procedure. The first two steps follow the WHO step-by-step approach, however the suggested third step in endometriosis management would be to add TCAs for neuropathic pain. Metamizol and opioids should be reserved for short-term use in case of acute pain. Muscarinic receptor antagonists are accepted treatment for bladder endometriosis. The use of COX-2 inhibitors is presented as an option in medical pain management. The use of magnesium hydroxide is recommended with all types of pain management and PPI's can be prescribed with NSAIDs use [29].

In addition to their general anti-inflammatory effects, certain analgesics can be used alongside surgical and/or hormonal treatments and may help prevent complications associated with chronic pain such as peripheral and central sensitization. On the other hand, NSAIDs specifically can give gastrointestinal and cardiovascular side effects which should be considered [9,11,12]. Although NSAID use is commonly accepted as an option for medical endometriosis-related pain management, also among our experts, the recommendation of the ESHRE guideline is very weak and based on one small randomized controlled trial [26]. Regarding COX-2 inhibitors, it is known that COX-2 is synthesized in low levels under normal conditions and can vary during the menstrual cycle. In women with endometriosis, COX-2 can be overexpressed in endometrial glandular epithelium and stroma [30]. Together with Prostaglandin E2 (PGE2), an important immune response regulator, it forms a cascade that plays a key role in endometriosis-related pain, ectopic implantation, growth of endometriosis lesions, angiogenesis and immunosuppression. Therefore, COX-2 inhibitors may not only be effective in reducing endometriosis-related pain but may also play a role in decreasing micro vessel density, macrophage count and VEGF/Flk-1 expression [30]. Similarly, the guideline did not make a recommendation regarding central neuromodulators. Unlike conventional analgesics, these primarily modulate pain through central nervous system pathways rather than peripheral inflammatory mediators. Anticonvulsants (e.g., gabapentin and pregabalin), TCAs (e.g., amitriptyline, nortriptyline) and SSRI's (e.g., duloxetine) have all shown promising results in medical treatment of endometriosis-associated pain. However, randomized studies have not found them superior to placebo in pelvic pain management and they are sometimes associated with severe, dose-limiting side effects [26]. Amitriptylin is preferred for its centrally acting properties, thereby providing an additional analgesic effect but should be dosed gradually to prevent overdose. Despite its efficacy, pregabalin can cause side-effects such as sleepiness, dizziness and headache. It should be tapered off under medical supervision if ineffective due to the risk of severe epileptic seizures [31]. All this underlines the importance of performing large, randomised prospective studies on the use of pain medication in endometriosis-related pain treatment.

While our main focus was pharmacological pain management, we also briefly considered self-management strategies and pain education, consistent with the biopsychosocial model of pain [5]. Previous studies found that incorporating self-management strategies, such as dietary interventions, yoga, mHealth or acupuncture, can improve quality of life (QoL) in endometriosis patients by enhancing self-efficacy [32]. The perception of control over health outcomes correlates with enhanced goal-setting and persistence. Individuals with greater self-efficacy demonstrate improved pain coping strategies and a reduced disruption of daily functioning due to pain. O'Hara found that greater self-efficacy was associated with physical and mental quality of life [33]. This underlines the importance of studying the effect of endometriosis symptom management from a multimodal approach, which not only focuses on the effect on symptoms but also other patient factors such as self-reliance societal participation [34].

Strengths and limitations

Our eDELPHI procedure has several strengths. First, a multidisciplinary expert consensus meeting preceded the first eDELPHI procedure, guided by an independent expert moderator. This ensured that a flowchart was developed which addressed medical pain management from all areas of expertise. Furthermore, consensus was reached on all but one question after two eDELPHI rounds. This might have prevented response fatigue and might have been achieved due to clear, well-designed questions. Finally, several reminders were sent to ensure that respondents came from both fields of expertise and that opinions from those in round one were also included in round two. However, there are also some limitations. First, 17 anesthesiologists initially responded to the first eDELPHI round, but only two of them met the inclusion criteria. Only one of these two anesthesiologists also responded to the second eDELPHI round. This has led to consensus being based on less variable expert opinions. Second, only 65 percent of the responding experts from round one also responded to round two. This might have been due to perceived redundancy, time constraint or voluntary participation. Furthermore, it is a known fact that fewer participants respond in the second round versus the first round. This might have contributed to attrition bias, reducing the diversity among respondents. It might also have reduced the robustness of findings, as the consensus of round 2 was based on fewer expert opinions. Finally, the eDELPHI was performed among Dutch healthcare providers. Therefore, these results cannot be extrapolated to endometriosis patients worldwide. This eDELPHI can be used as a knowledge basis for an international DELPHI procedure or future clinical studies.

CONCLUSION

Through this eDELPHI procedure, a flowchart outlining subsequent steps in medical pain management in endometriosis was developed and evaluated by experts in OBGYN and

Anesthesiology. It was aimed to lay the groundwork for an international consensus and future clinical studies on medical pain management in endometriosis. The fact that the use of certain types of medication is based on limited scientific evidence underlines the importance of future studies on medical pain management for endometriosis. Furthermore, it is important to take the complexity of endometriosis treatment into account when accessing their efficacy. Incorporating self-management strategies may provide a solution by enhancing patients' self-efficacy, thereby amplifying the impact of symptom management on quality of life and facilitating reintegration into society**.**

QR code to article for supplementary materials



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Chapter 6

Spinal Cord Stimulation for intractable visceral pain originating from the pelvic and abdominal region: a narrative review on a possible new indication for patients with therapy-resistant pain.

Annelotte van Haaps, Matthanja Bieze, Leonardo Kapural, Sean Li, Kris Ferguson, Ralph de Vries, Michael E Schatman, Velja Mijatovic, Jan Willem Kallewaard

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ABSTRACT

Aim: Visceral pain, characterized by pain that is diffuse and challenging to localize, occurs frequently and is difficult to treat. In cases where the pain becomes intractable despite optimal medical management, it can affect patients' Quality of Life (QoL). Spinal Cord Stimulation (SCS) has emerged as a potential solution for intractable visceral pain.

Purpose: In this narrative review, we collected all evidence regarding the efficacy of SCS for visceral pain across various underlying conditions.

Methods: A comprehensive literature search was conducted in PubMed, Embase, and Web of Science in which articles published from October 1st, 1963 up to March 7th, 2023 were identified.

Results: Seventy articles were included in this review of which most were retrospective cohort studies, case series and case reports. The studies, often with a small number of participants, reported on SCS for chronic pancreatitis, anorectal pain and bowel disorders, gynaecological diagnoses, visceral pelvic pain, urological disorders and finally general visceral pain. They found positive effects on pain and/or symptom relief, opioid consumption, anxiety and depression and QoL. Complications occurred frequently but were often minor and reversible.

Conclusion: Better screening and selection criteria need to be established to optimally evaluate eligible patients who might benefit from SCS. A positive outcome of a sympathetic nerve block appears to be a potential indicator of SCS effectiveness. Additionally, women receiving SCS for endometriosis had a better outcome compared to other indications. Finally, SCS could also relief functional symptoms such as voiding problems and gastroparesis. Complications could often be resolved with revision surgery. Since SCS is expensive and not always covered by standard health insurance, the incorporation of cost-analyses is recommended. In order to establish a comprehensive treatment plan, including selection criteria for SCS, rigorous prospective, possibly randomized and controlled studies that are diagnosis-oriented, with substantial follow-up and adequate sample sizes, are needed.

INTRODUCTION

Visceral pain is characterized by pain that is diffuse and challenging to localize, frequently originating from the midline of the body, the lower sternum or upper abdomen. It is thought that the prevalence of visceral pain exceeds 20% of the global population [1]. In 2016, visceral pain from the chest, abdomen or pelvis accounted for more than 25 million emergency room visits and 2.5 million hospitalizations in the United States [2]. Visceral pain can be referred, where pain from visceral organs can be perceived in areas other than their source. For example, pain originating from the bladder can radiate to the perineal area and is caused by viscero-somatic convergence in the spinal cord [3-5]. Visceral pain results from activation of nociceptors of the thoracic, pelvic, or abdominal visceral organs and typically originates from inflammation, distention, and ischemia. Pain is induced when nociceptors surrounding visceral organs are stimulated as a result of inflammation and recurrent distention. When it occurs suddenly, visceral pain is frequently associated with clinical conditions such as appendicitis, cholecystitis, or ulcers. When occurring chronically, it is generally associated with clinical conditions such as endometriosis, pancreatitis or chronic pain originating from the bladder or bowel. Some cases may have no identifiable substrate and are considered idiopathic or functional visceral pain [1]. The sympathetic (thoracolumbar) and parasympathetic (craniosacral) nervous system innervates all thoracic and abdominal organs, other than the pancreas. The viscera are innervated through a complex network of two sets of nerves, either through vagal and spinal nerves, or through two anatomically distinct sets of spinal nerves [6].

Management of visceral pain presents significant challenges. While prioritizing the resolution of the underlying (chronic) inflammation or distention is crucial, the need for pain management becomes necessary in many cases. The effectiveness of combining paracetamol with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for pain treatment in reducing visceral discomfort has been established [7,8]. Opioids may be administered as needed, although their dosage requires caution due to the risk of opioid induced hyperalgesia – namely abnormal sensitivity to pain – which can mimic pain associated with progression of the underlying pathology. Consequently, this can result in the worsening of visceral pain. In addition, the concomitant administration of antidepressants or antiepileptic medication with opioids may reduce visceral pain [8]. Finally, neurolytic blocks such as a plexus hypogastricus block, plexus coeliacus block, or splanchnic nerves block, along with radiofrequency ablation, can aid in the reduction of visceral pain [9].

Despite the implementation of optimal medical interventions, chronic visceral pain has the potential to become refractory, thereby exerting a negative impact on the overall quality of life (QoL) experienced by the affected individuals. A treatment that might offer a solution is Spinal Cord Stimulation (SCS). First introduced in 1967 for chronic intractable cancer pain, SCS is a minimally invasive therapy offering pain relief for a growing number

of conditions [10]. In SCS, electric fields are created between metal contacts which are placed in the epidural space. These applied fields can, based on tissue properties near the electrode, change the electrical potential across membranes. The electrodes are typically placed in close proximity to the physiological midline of the dorsal columns. The electrical stimuli activate dorsal column axons, resulting in orthodromic and antidromic transmission of action potentials. These action potentials generate segmental and supraspinal effects, resulting in pain relief. The electrical stimuli can be administered via various wave forms, which can be characterized based on pulse amplitude, frequency, width and electrodes activation sequence [11,12]. For visceral pain, SCS can block the sympathetic pain pathway that carries nociceptive information in small fibres, thereby preventing the pain signal to arrive in the thalamus and cerebral cortex and thus removing the pain [13,14].

In the Netherlands, the number of diagnoses for which SCS is covered by health insurance is limited. Insurance companies cover expenses in cases solely associated with chronic pain caused by Persistent Spinal Pain Syndrome (PSPS) Type 2, Failed Neck Surgery Syndrome (FNSS), Complex Regional Pain Syndrome (CRPS), Diabetic Polyneuropathy with Small Fibre Neuropathy, or medically refractory Chronic Cluster Headache [15]. Although several studies have suggested that SCS is effective in reducing visceral pain, SCS is not yet covered in the Netherlands for this indication by any Dutch health insurer. This because SCS for visceral pain currently does not comply to with the state of research and practice, as determined by the Dutch healthcare institute. Only indications that comply with the determination of the healthcare institute, are covered by healthcare insurance. However, according to the systematic review by Woodroffe et al. (2020) [16] SCS has been successfully used for pain associated with chronic gastrointestinal (GI) motility disorders such as irritable bowel syndrome (IBS) or gastroparesis and post-surgical visceral hyperalgesia (for example status post Nissen fundoplication, gastric bypass, bowel resection, post-cholecystectomy, among others). For the male patient population, SCS has been successfully applied for chronic orchialgia (testicular pain) which, for example, can be caused by prostate carcinoma or a ruptured epididymis. For the female patient population, it has been successfully applied for chronic pelvic pain that can be caused, among other things, by long-standing endometriosis. The authors noted that recent studies suggest it might be very effective in treating visceral pain. However, scientific evidence supporting this inference is limited [16].

In this narrative review, our primary aim is to provide a comprehensive overview of the existing literature on the efficacy of SCS in treating visceral pain. By analyzing the current literature, we aim to contribute to the understanding of SCS as a potential therapeutic option for various visceral pain conditions and to identify the existing gaps in scientific evidence.

METHODS

This narrative review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The narrative review was retrospectively registered in the PROSPERO international prospective register of systematic reviews (CRD42023448103; registration date 13th of July 2023). To identify all relevant publications, we conducted systematic searches in the bibliographic databases PubMed, Embase.com and Web of Science (core collection). Articles published between October 1st 1963 until March 7th, 2023 were found. The systematic search was conducted in collaboration with a medical librarian. The references of the identified articles were searched to ensure that no relevant literature was excluded. Duplicate articles were excluded by a medical information specialist using Endnote X20.0.1 (Clarivatetm), following the Amsterdam Efficient Deduplication (AED)-method [17] and the Bramer-method [18]. Full search strategies for all databases can be found in Appendix A. Three reviewers (MB, JWK and AHA) independently screened all potentially relevant titles and abstracts for eligibility. Full texts were screened when articles were considered eligible for inclusion based on the title and abstract. When there was a difference in judgement between the three reviewers, a consensus procedure was performed by discussing the article, its outcome measures and the reasoning behind the different opinions. This was done until consensus was reached.

There are considerable difficulties in studying patients with refractory chronic pain and SCS: the patient group is small and heterogeneous, SCS is expensive and not readily available. These circumstances demand a wide inclusion of studies with various designs. Therefore, reports describing adult patients with all causes of visceral pain employing SCS from 1967 until March 7th, 2023 were included in this narrative review. Clinical trials were ranked highest, followed by cohort studies and finally, case series or reports. Comparative studies and non-comparative proof of concept and feasibility studies were also included. We included articles in Dutch and English. Technical reports, anatomical descriptions, dose finding studies, studies comparing neurostimulator modalities, and studies comparing various approaches were excluded. We focused on the population of patients with chronic refractory abdominal and pelvic visceral pain in whom SCS was employed to treat chronic pain. All articles were reviewed for the following outcomes: effectiveness (pain scores, pain reduction, reduced demand for systemic analgesic drugs, and patient satisfaction); complications (for example nerve injury, lead migration and malfunction, infection); functional recovery (for example gastropareses, bladder function and voiding) and QoL. Other relevant findings (for example medical costs) were also recorded and summarized (Table 1).

RESULTS

The literature search generated a total of 10,854 references. After removing duplicates, 7460 references remained (Flowchart Figure 1). A total of 56 reports were included from the primary search, and 14 were added after thorough examination of the reference lists of included studies. An overview per study can be found in Table 1. The results are summarized according to diagnosis. We identified several randomized controlled trials. However the majority of the included studies were observational studies, case series and case reports, with low to very low quality evidence. Therefore, in addition to the heterogeneity of study outcomes, the results could not be compared quantitatively in a meta-analysis.

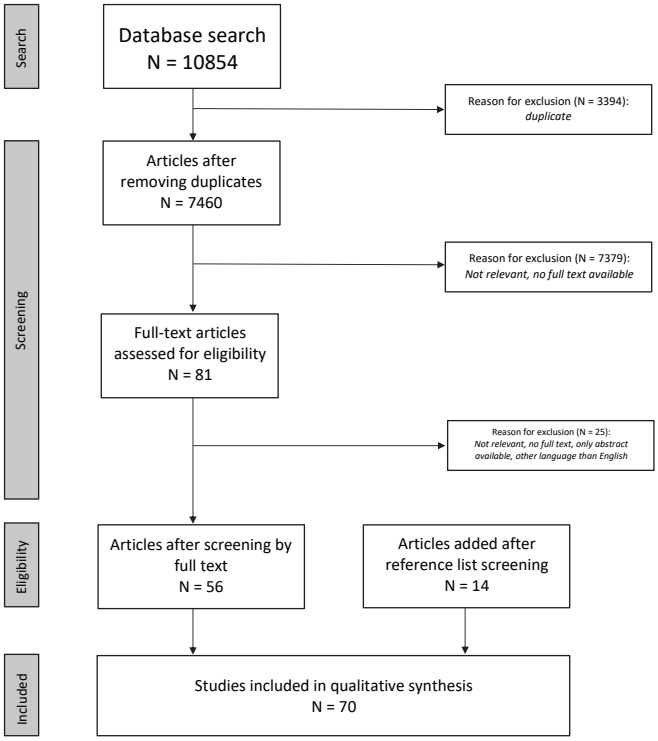

Figure 1. Results of the literature search and flowchart of all included articles.

Spinal Cord Stimulation for Chronic Pancreatitis, Table 2

Chronic pancreatitis often results in chronic pain, which intensifies during episodes of active inflammation, while normal pancreatic function further deteriorates [19]. SCS is rarely used in patients with chronic pancreatitis and is currently not recommended. However, studies performed on patients receiving permanent SCS for chronic pancreatitis concluded that pain scores decreased significantly, Pain Disability Indices (PDI) improved,

opioid consumption was reduced, and ADLs improved [13,20-26]. Complications that were observed included infection and lead migration, both of which necessitated the revision or removal of the device. Therefore, it could be concluded that when chronic pain from pancreatitis is drug therapy resistant and when management becomes intractable SCS can be a beneficial minimally invasive strategy prior to contemplating a surgical intervention [27]. The same can be considered for retractable pain associated with Sphincter of Oddi dysfunction, described in a case report by Mamaril-Davis et al. [28]. They found that pain scores, QoL, sleep and appetite improved after implantation of sacral neuromodulation (SNM), with 90% pain relief at 18 months follow-up. No complications were reported. Patient selection for treating pancreatitis with SCS is challenging, due to the absence of large RCTs and comprehensive inclusion- and exclusion criteria. Until these criteria are more firmly established, most clinics and studies continue to use a test trial period prior to permanent implantation. The PANACEA trial (NCT03595241), is the first randomized clinical trial evaluating the effectiveness of SCS for patients with chronic pancreatitis [2929](29). They recently reported their four-month follow-up and found significant reduced pain scores when SCS was applied, compared to conservative medical management. However, we are still awaiting their definitive results [30].

Spinal Cord Stimulation for Pelvic Pain

I Anorectal Pain and Bowel Disorders, Table 3

Functional anorectal pain disorder (also known as chronic idiopathic anal pain) is a diagnosis per exclusionem. It is diagnosed only after excluding all other causes of rectal pain with a structural cause such as active ischemia, fissure, inflammatory bowel disease, infection, hemorrhoids and tumors. In the limited studies with small sample sizes that are available, drastic improvement in pain scores and patient global perceived effect (PGPE) have been demonstrated [31-33]. However, complications such as infection, lead migration, and discomfort at the stimulator site are frequently observed. The authors of these limited-scale studies acknowledge that this cohort of patients, similar to numerous patients with chronic pain, is not a one-size-fits-all category. Consequently, personalized approaches for patients, such as the use of Spinal Cord Stimulation (SCS), are required when conventional treatment has been proven ineffective [32]. The different treatment options were evaluated in a network meta-analysis by Byrnes et al. [34] that included 27 studies on the treatment of anorectal pain, of which six studies reported on treatment with sacral neuromodulation (SNM). They concluded that intramuscular injection of triamcinolone and SNM were likely to be clinically effective, with a surface under the cumulative ranking (SUCRA) score of 0.79 and 0.74, respectively. Compared to other treatment methods, SNM showed superior efficacy in reducing pain scores. However, it should be noted that the interpretation of these findings is limited due to the inclusion of low-quality research and the large contribution of the study by Rongqing et al. who included 120 patients without implantation of a permanent device [35]. A case series by Dudding et al. (2013) permanently

implanted three patients for idiopathic anal pain, which was beneficial in only one of their three patients[36]. Bowel disorders such as gastroparesis, irritable bowel syndrome and fecal incontinence might benefit from SCS, as is described in case reports of patients who suffered not only from intractable abdominal pain, but also from debilitating gastro-intestinal symptoms [37].

All symptoms resolved following initiation of SCS [38,39]. In patients with gastroparesis who were studied prospectively [40] and retrospectively [41], both traditional tonic and 10 kHz sub-threshold stimulation was not only effective in improving pain scores but also in reducing the occurrence of nausea and vomiting [40,41]. However, significant improvements in pain scores, nausea and vomiting occurrence were achieved when 10 kHz SCS was used as opposed to low-frequency, traditional tonic stimulation. Pain severity scores in patients stimulated at 10 kHz (n=12) decreased from 8.4±1.2 cm at baseline to 2.6±3.2 cm at the latest patient visit ($p<0.001$), whereas the traditional SCS group (n=11) scores reduced from 8.9±1.4 cm at baseline to 3.8±3.0 cm ($p=0.001$). Similarly, the number of 'nausea days' per month showed a reduction of over 50% for both study groups, although 10 Hz was significantly better ($p=0.035$) regarding this metric [41]. Three studies have reported on the efficacy of SCS for IBS symptoms. Compared to the baseline scores, each study reported (often significant) improvement in pain (measured using VAS, scale 0-10cm), in pain frequency, in anorectal comfort, in IBS-specific symptom scores (measured by the Gastro-intestinal Syndrome Rating Scale), and finally in IBS-specific QoL [37,42,43]. The reported complications included infection, lead migration, pain at the implantation site or loss of device efficacy. Given the current evidence on the "brain-gut axis" [44,45], it is plausible to propose neurostimulation as a treatment option for severe cases of irritable bowel syndrome, which is considered a dysregulation of the central nervous system [38].

II Gynaecological, Table 4

Chronic Pelvic Pain (CPP) shares a similarity with the above-mentioned pain syndromes, as it is a diagnosis per exclusionem. Nonetheless, the condition is debilitating. Endometriosis is no diagnosis per exclusionem and is, apart from CPP, additionally associated with symptoms of dysmenorrhea, dyspareunia, dysuria and dyschezia. Because of their experienced pain, patients may undergo a hysterectomy or otherwise invasive surgery, which could be ineffective in removing all pain or might even result in an aggravation of pain [46]. CPP is a multifactorial condition that affects psychological, psychosocial, cultural, and economic factors. Furthermore, the pelvic region has a complex innervation and chronic pelvic pain may arise due to central sensitization. This condition is marked by the recurrent or extended stimulation of nociceptors, leading to a decreased threshold for activation. As a result, patients may experience pain even when there is no pain substrate [47] thereby presenting a significant challenge in terms of treatment [48]. SCS can be effective in selected patients as it is minimal invasive, making it a viable option to consider before proceeding with a more permanent surgical or neurolytic procedure [49,50]. After implanta-

tion of SCS, patients reported an improvement in QoL, pain severity scores, Pain Disability Index (PDI) scores, Beck Depression Inventory (BDI) scores, and functional symptoms. In addition, patients exhibited a high level of satisfaction, with some even expressing a profound level of contentment, in response to SCS treatment [51-54].

Also of note in this patient cohort there was a high incidence of complications. Some patients underwent explantation of the device due to infection, local pain, device failure, lead migration, a broken lead, excess granulation tissue, the need for an MRI for non-MRI compatible devices, allergy, and gradual loss of effect in the older wave form units. A Finnish national study confirmed this, where they found similar adverse events despite overall positive results. In their study, they determined that women with SCS for CPP related to endometriosis reported superior success rates compared to women with SCS for idiopathic CPP (75% vs 41% resp., P=0.026), with a high percentage of advancement to permanent implantation and strong symptom improvement following implantation. However, the IPG was removed in six of 50 participants (12%) due to loss of efficacy (4/6), pain (1/6) or infection (1/6) [55]. As was already stated in the Cochrane review in 2000: '*Given the prevalence and the health care costs associated with chronic pelvic pain in women, randomised controlled trials of other medical, surgical and psychological interventions are urgently required*' [56]. Unfortunately, these are currently lacking in the literature. Five previous studies determined that Sacral Nerve Stimulation (SNS), SCS and/or Peripheral Nerve Stimulation (PNS) were effective in reducing endometriosis-related pain symptoms such as CPP and dyspareunia, anal pain, and intestinal constipation. They also found high patient satisfaction, an improvement of QoL, a reduction in the use of pain medication, an improvement in Oswestry Disability Index (ODI) scores, Hospital Anxiety and Depression Scale (HADS) scores. Finally, they found improvements in social participation where women were able to work again, take part in social activities and travel [57-61]. The complication most frequently reported was electrode migration. At present, there are three trials recruiting (in France, the Netherlands (NCT05558540) and Turkey) participants that are treated with SCS and suffer either from pelvic pain related to endometriosis or are suffering from CPP in general.

III Urological Disorders, Table 5

Despite the number of studies being limited, most prospective studies on SCS for pelvic pain focus on urological disorders and universally conclude that well-selected patients respond favorably to SCS with improved pain severity scores, reduced CPP and improved voiding symptoms [62-74]. Their results seem sustainable in the absence of complications, which is substantiated by studies with longer follow-up periods [68,75,76]. Further, when comparing it to a control group with similar disease presentation, SCS improves pain severity scores and overall outcomes [77]. However, an older study by Elhilali et al. demonstrated that not all functional urological problems are successfully treated with SNM and treatment can lose its efficacy over time [78]. However, this study was published in

2005, at a time when advanced wave forms were unavailable, so application to current clinical realities is questionable. Complication rates vary between studies, with revision rates being as high as 50%. These were primarily attributed to loss of efficacy, local pain at the implant site, painful stimulation, and the necessity for battery revisions. In some studies, the explant rate was as high as 27% and seems to be attributed to a more practical concern, namely the need for an MRI [79]. This challenge was not exclusive to SCS for urological disorders, but rather a recurring issue encountered in the context of any implanted device [80]. However, the significance of this matter has diminished in light of the recent emergence of MRI-compatible technologies. Even though reported revision rates were relatively high, SNM should be considered prior to proceeding with any invasive surgical intervention [76,81].

Aiming to optimize SCS treatment, Everaert et al. (2004) studied the 1-stage versus 2-stage SNS for bladder dysfunction where a lower rate of treatment failure was demonstrated in the 2-stage implant. Moreover, the trial procedure has been subject to innovation. According to Powell et al. (2010) a greater number of patients have a successful trial with quadripolar lead placement compared to a single test lead. However, the benefit of long-term treatment was equal in both groups [82,83]. In their study, Peters et al. compared pudendal nerve stimulation to sacral neuromodulation and calculated that 77% of patients (13/17) chose pudendal nerve stimulation following blinded testing. Nevertheless, irrespective of the patients' preferences, long-term outcomes were comparable in both cohorts [84]. A noteworthy observation is the association between higher pain scores, the Interstitial Cystitis Symptom Problem Index (ICSPI) scores and the levels of urine chemokines [85]. Follow-up after device implantation demonstrated a decrease in ICSPI with a concomitant decrease in urine chemokines, which implies a role of chemokines in neurophysiological signaling in bladder pain and -function [86].

A large retrospective cohort study examined the Finnish experience and collected data since the initiation of SCS in Finland in 1996. This study included the application of SCS for three diagnoses: urgency-frequency syndrome, urinary retention, and painful bladder syndrome/ interstitial cystitis (PBS/IC) [87]. Although over 50% of their patients did not receive permanent implantation (74/180), all three groups experienced benefit from SCS with improvement in voiding symptoms, a reduction in the number of catheterizations and in pain severity. The results of the study furthermore suggested that younger patients are more likely to benefit from SCS. For some indications, alternative treatments may be more cost-efficient as financial costs of SCS are significant. However, research comparing health care utilization and cost-effectiveness associated with SCS to other therapies is strongly needed to understand relevant economic issues. For example, Botulinum A toxin is a more cost-effective alternative to SCS for patients with urge incontinence and should therefore be tried first [87,88]. Patients implanted with SCS reported a high rate of satisfaction (90%), despite the limitations and complications of the treatment. Satisfaction with

SCS was positively correlated with the ability that the patient could personally adjust the device and whether the patient was still active and/or working. The presence of two or more pelvic floor comorbidities was negatively correlated with the patients' satisfaction with SCS [89]. Also, given that chronic pain and mental health are often intertwined, most medical institutions that implement SCS have established a close collaboration with the psychologic or psychiatric departments. For some, the coexistence of pain and depression is considered a contra indication for implantation of a neuromodulator. Nevertheless, the use of SCS has shown potential in improving depression scores [73,90], raising a complex question regarding causality. Additionally, Killinger et al. demonstrated that patients who manifested major depressive symptoms (PHQ-8 scores ≥10) did not display an inferior response to SCS [91].

Various Causes of Pelvic Pain, Table 6

Not all studies make a distinction between different causes of CPP. These studies include various patient cohorts, predominantly those who present cohorts with combined surgical, gynaecological and urological symptoms. Their results were similar to those mentioned in the previous sections: SCS resulted in reduced pain and improved functional symptoms. Patients with chronic pelvic pain following hysterectomy and those with only one pelvic comorbidity reported better results compared to other, or multiple pelvic comorbidities [92,93]. One case report suggests that SCS may be effective in reducing CPP secondary to multiple Tarlov Cysts, which were previously worsened by surgical treatment as well as in reducing the use of analgesics [94]. Another case report suggested that SCS may be effective in reducing CPP secondary to multiple pelvic fractures [95]. Various pelvic disorders were combined in the study by Hernandez-Hernandez et al. who demonstrated substantial improvements in pain severity scores, functional symptoms and QoL. However, complication rates were as high as 40.6%, which resulted in 5/64 patients undergoing device explantation. [96] This is relatively low compared to the study by Al-Kaisy et al., which identified explant rates of SNM devices of 17.8% after five years and of 25.2% after ten years, where explantation was performed because of various indications [97]. An attempt to develop a management algorithm for patients with CPP was published by Bridger et al. in 2021 [98]. Over the course of seven years, 233 patients with CPP were referred, 153 were included in the protocol, and only eleven underwent SCS. These patients experienced neuropathic pain, penile pain, painful bladder syndrome, small fibre neuropathy, and neuralgia. The authors intended to compare the SCS group to the non-SCS group, but patient numbers were too small to allow a comparison. Nevertheless, it appeared that SCS was more effective in treating neuropathic pain compared to other treatment options [98].

A pilot study across multiple etiologies for chronic pelvic pain (predominantly post-surgical CPP, post-partum CPP, and interstitial cystitis) reported effective use of high frequency SCS [99] for patients with CPP, with 10/14 (71%) patients who received a permanent

implant reporting ≥50% pain relief at twelve months. This high-frequency 10-kHz therapy is paresthesia-free, although it requires dedication to uncover the optimal programming. In addition, there frequently is a delay in analgesic onset (12-48 hours or longer), which is distinctly different from low-frequency therapy [100,101]. In their study, Kapural et al. studied the efficacy of high-frequency therapy in providing pain relief and compared it to low-frequency Spinal Cord Stimulation (SCS). Their findings indicated that high-frequency therapy may be more successful than low-frequency SCS in alleviating pain, not only in patients with chronic back and/or leg pain, but also in those experiencing chronic abdomen pain. In the examined patient cohort no paresthesia was reported [40,102-105]. Although high-frequency therapy is not universally implemented in all European countries, it is implemented in the Netherlands. A study from the Netherlands concluded that the use of bilateral stimulation over multiple levels could be more effective because chronic pain can result in recruitment and upregulation of additional fibers [106].

Visceral Pain in General, Table 7

In some studies, SCS for visceral pain in general was the terminus a quo, thereby including a wide range of underlying conditions. These conditions included postsurgical pain, post-childbirth, interstitial cystitis, pancreatitis, inflammatory bowel disease, endometriosis, renal calculi, liver pathology, trauma, pudendal neuralgia and post infection chronic pain. Overall, all studies reported improved pain severity scores and PDI, decreased analgesia consumption and improvement in PGIC, QoL, SF-MPQ-2 scores, GAF scores, daily activities and mood [26,40,41,107-112]. The initial prospective SCS study for chronic and refractory abdominal pain that received IDE approval from the FDA was performed by Kapural et al. and used a 10 kHz SCS. The authors documented an improvement in pain severity scores (in VAS, scale 0–10cm) of 6cm from baseline, a reduction in PDI and opioid usage and finally a profound improvement in patient satisfaction twelve months after implantation [40]. Despite these excellent prospects of SCS, no standard approach to chronic abdominal pain is currently governed [16]. Both ventral and dorsal horn implantation were effectively applied. However, ventral stimulation was preferred by four patients with dual leads and was lower for ventral stimulation. This was likely due to the cerebrospinal thickness in the dorsal and ventral space [108]. However, recent studies did not confirm this finding. For dorsal column stimulation, a "sweet spot" for treatment of visceral pelvic pain is suggested at the level of T12 due to the segmental suppression of sympathetic outflow to the pelvis via the hypogastric plexus [109]. Kapural et al. also observed that the efficacy of sympathetic nerve blocks may serve as a potential indicator for the success of SCS. Six patients who failed the trial period and one patient who had the device removed because of ineffectiveness shared a poor response to the preceding sympathetic nerve block [109]. This was supported by the study by Hord et al. who treated CRPS with SCS.

They found that twelve patients with a positive sympathetic nerve block experienced strong and long-lasting pain relief, whereas only one (33.3%) out of three patients with a

negative response to the nerve block reported substantial pain relief [113]. Therefore, caution is advised when implanting patients subsequent to a failed sympathetic nerve block. There is a potential oversight of patients with visceral pain in our narrative review, since certain cases may be obscured within studies encompassing diverse patient cohorts. Individual patients are often lost in a large group, as no details are provided per subgroup. For example. the series by Kumar et al. reported on 410 patients treated with SCS for various underlying chronic pain conditions. Over 200 patients were treated with SCS for Persistent Spinal Pain Syndrome (PSPS) Type 2 in addition to six patients with perirectal pain. Of these patients, four ultimately received a permanent SCS implant with long term success [114]. No further mention was made regarding this subgroup. The authors strongly supported the use of SCS, as they noted its reversibility, minimal invasiveness, low complication rate, and effectiveness.

CONCLUSION

This narrative review provides an overview of the current evidence on SCS for visceral pain across a wide range of underlying conditions. Most studies we identified were of low quality, with many retrospective cohorts, case series and -reports. This review highlights the necessity for improved screening and selection criteria to evaluate eligible patients who will benefit most from treatment with SCS. Multidisciplinary involvement is essential for finding the best treatment option for each patient. A noteworthy observation from several studies is the potential of using preceding positive responses to sympathetic nerve block as the basis for selecting patients for SCS. Patients who do not experience a positive effect from sympathetic nerve blocks might not necessarily respond to SCS, even after a positive trial. Some general studies on SCS suggest a positive correlation with younger age and efficacy of SCS for urological disorders. Other studies indicate a negative correlation between a greater number or complex pelvic comorbidities and the efficacy of SCS. Patients with endometriosis might have more favorable results in comparison to individuals with other etiologies of CPP. Furthermore, SCS can successfully treat both chronic pelvic pain and functional symptoms. These include disabling bowel and voiding problems in a selected group of patients. However, high complication rates negatively affect the applicability of SCS, particularly with older units. Steps towards reducing these complication rates should be made, as these directly impact the quality of life of patients. Moreover, some studies suggest that the positive effects of SCS gradually decline over time. However, this concern appears to be mitigated with the introduction of more advanced waveforms. Finally, this review acknowledges that costs are a major concern, as SCS is expensive and not commonly covered by standard health insurance in the Netherlands and on a global level. We stress the need for sound, prospective, possibly randomized and controlled studies, with an adequate number of patients and substantial

follow-up, to determine a pain treatment plan including selection criteria for SCS. It is recommended to incorporate cost analyses into future studies.

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Chapter 7

Spinal Cord Stimulation for intractable, visceral pain associated with endometriosis: results on a feasibility study.

Annelotte van Haaps, Jan Willem Kallewaard, Matthanja Bieze, Misha Erwteman, Annemiek Nap, Markus Hollmann, Anneke Schreurs, Velja Mijatovic

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ABSTRACT

Objectives: Endometriosis, an estrogen-dependent chronic inflammatory disease, can cause visceral pain. Owing to its chronic nature, treatment can be challenging and insufficient in reducing all symptoms despite adequate management. Spinal-cord stimulation (SCS), a well-established treatment, could be used in treating intractable, endometriosis-related visceral pain and thereby improve quality of life (QoL).

Methods and Materials: A prospective, unblinded feasibility study (NCT05558540) was conducted between May 2022 and January 2025. We included patients with endometriosis reporting pain scores ≥ 5 (numeric rating scale [NRS], 0-10) who are experiencing dysmenorrhea, dyspareunia, and/or chronic pelvic pain (CPP), with a clear neurologic examination and approval for SCS during multidisciplinary consultation. All participants received a Boston device with two 16-contact Infinion CX leads placed between T8 and T12, with a 14-day trial period before permanent implantation. Inclusion stopped when seven participants experienced ≥ 50% symptom improvement at 6-month follow-up. Pain symptom reduction (in NRS) was used as the primary outcome. Secondary outcomes included change in QoL (NRS; Endometriosis Health Profile-30 [EHP-30]), Short Fatigue Questionnaire, Pain Catastrophizing Scale, and analgesic use. Data were collected through questionnaires and during examination visits.

Results: Nine participants underwent SCS, and after a successful trial period, all had a permanent implantation. Improvement in general and worst pain, and of dysmenorrhea, CPP, dysuria, and dyschezia was observed when comparing baseline with different follow-up moments. Improvement was found in self-reported QoL scores and in all but one of the EHP-30 core domains. All participants but one were able to reduce their analgesics. One participant underwent device explantation owing to lack of effect at 12-month follow-up.

Conclusions: SCS reduced intractable, endometriosis-related visceral pain and improved QoL. Because no sample size calculation could be performed, the results should be interpreted with caution. We emphasize the need to further study the application of SCS for endometriosis by performing randomized studies, which also includes a cost-analysis.

INTRODUCTION

Endometriosis is an estrogen-dependent, chronic inflammatory disease that is characterized by the presence of endometrium-like tissue outside the uterus [1, 2]. With a prevalence between 2% and 10% in the female population of reproductive age, this extrapolates to 190 million women globally [2]. Symptoms associated with endometriosis include dysmenorrhea, dyspareunia, dyschezia, dysuria and infertility [2]. Moreover, endometriosis can cause chronic pelvic pain (CPP). A previous study found that ≥33% of women who undergo laparoscopic examination for CPP were diagnosed with endometriosis [3]. Symptoms can, together with pain intensity and pain cognition, reduce quality of life (QoL) and negatively affect daily activities [4]. Endometriosis also has large societal impact through increased health care costs and loss of productivity, comparable to other chronic diseases such as diabetes mellitus type 2 or rheumatoid arthritis [2, 5-7]. There are several mechanisms believed to generate endometriosis-related pain, which contributes to the complexity and chronic nature of the symptoms [8-12]. The mechanisms may be the reason patients often experience pain that is disproportionate to the condition itself, in addition to the emotional distress that can affect both their work and personal lives [13]. Furthermore, the complexity presents challenges for effective treatment. Standard endometriosis treatment includes hormonal therapy, surgery, and conventional pain management but can nonetheless be insufficient in resolving all endometriosis-related pain [2]. A previous systematic review stated that, independently of the type of endometriosis management, up to 59% of women still experienced symptoms after treatment and up to 19% reported no symptom reduction. Moreover, up to 34% of women reported symptom recurrence after treatment cessation [14]. Furthermore, surgical treatment of endometriosis lesions can cause chronic postoperative abdominal pain [15].

Spinal-cord stimulation (SCS) is a well-established treatment for neuropathic pain. Although the application of SCS for endometriosis has not yet been reimbursed by health insurance, it could offer a novel treatment strategy for women with intractable, endometriosis-related visceral pain [16]. In recent studies the application of SCS for CPP, in some cases associated with endometriosis, yielded reduced pain scores, decreased pain disability, and less depression, in addition to an improved QoL. However, evidence regarding the effectiveness of SCS in reducing visceral pain, more specifically endometriosis-related visceral pain, is limited, and broadening this knowledge is advocated [16, 17]. This study aimed to prospectively determine feasibility on the use of SCS in patients with intractable, endometriosis-related visceral pain and create a solid data foundation for a future large randomized controlled trial.

METHODS AND MATERIALS

Study Design

A prospective, unblinded feasibility study was conducted between May 2022 and January 2025 at the Academic Endometriosis Center of the Amsterdam University Medical Center (Amsterdam UMC) in Amsterdam, The Netherlands. Participants were recruited at the Amsterdam UMC and Rijnstate Hospital in Arnhem, a Dutch teaching hospital. Both hospitals are accredited level-2 specialized centers for endometriosis care and collaborate closely with a specialized pain management team. The study was approved by the institutional review board (METc number 2021_025#C2021629) and registered prospectively at the international clinical trials registry (reference number NCT05558540).

Women aged ≥ 18 years with a confirmed diagnosis of endometriosis during laparoscopic surgery or by radiologic imaging were considered eligible for inclusion. Eligible patients were identified by their treating physician who oversaw symptom management. This could be either a pain specialist or gynecologist, employed in the field of endometriosis care. After identification, the patient was discussed to assess eligibility during a multidisciplinary consultation (MDC) with specialists from the Department of Gynaecology and Pain Department. Patients were approached for study participation only when approved during an MDC. Patients had to report intractable endometriosis-related pain (on the numeric rating scale [NRS] 0-10) with scores of ≥5 in dysmenorrhea, dyspareunia, and/or CPP. All patients were previously treated by a gynaecologist and pain specialist when treatment options provided insufficient pain reduction. These treatment options included hormonal suppression of endometriosis progression and operations to remove all lesions but also pain management options including pain medication, transcutaneous electrical nerve stimulation, and neurolytic blockage. All treatment options that the participants underwent are listed in Table 1. Patients met the inclusion criteria for SCS, and neurological examination revealed no marked motor deficits [18]. General contraindications for SCS device implantation were used as the exclusion criteria for this study [19, 20]. Finally, pregnancy, in addition to a pronounced wish to conceive, the presence of a malignancy, an inability to use the SCS device, or previous neuromodulation therapy were exclusion criteria.

Implantation with SCS

After providing informed consent, the women were observed by the specialized SCS team of the Department of Anesthesiology at the Amsterdam UMC. Patients were implanted with the WaveWriter Alpha Spinal Cord Stimulator System (fast-acting subperception therapy (FAST), tonic, burst, 2-1,200 Hz), a rechargeable, remote controlled SCS device by Boston Scientific Corporation (Marlborough, MA). Two 16-contact Infinion CX leads were placed in the epidural space under conscious sedation and with continuous radiologic imaging. Perioperative paresthesia mapping was performed during surgery.

Lead placement was patient-specific but preferably between T8 and T12, with an aimed optimal coverage of T11. This placement was selected to cover the nn Splanchnici that run between T6 and L1 and are believed to innervate the viscera. All participants initially received stimulation through FAST. They were programmed with a frequency of 90 Hz and a pulse width of 210 ± 50 μs [21]. Patients received stimulation at or around T11. One participant requested a switch to paresthesia-based stimulation at 6-month follow-up, with good results. Patients first underwent a 14-day trial period, when the 2 16-contact infinion leads were connected to an external pulse generator (EPG). Pain reduction of ≥ 50% had to be achieved for the permanent SCS device to be implanted. Next, the EPG was removed, and the leads were connected to an internal pulse generator (IPG). Both procedures were performed at the day surgery center. Preparation for permanent implantation was performed during the first procedure, creating a pocket for the IPG, and tunneling the leads for connection to the IPG.

Patients visited the outpatient clinic according to standard local protocol for frequent examinations, that is, 1 week after trial implantation but also 1 week, 1 month, 3 months, 6 months, and 12 months after permanent SCS implantation. These examinations were performed by specialized nurses working at the Department of Anesthesiology of the Amsterdam UMC who are routinely involved in neuromodulation and were not involved in the study. They adjusted the stimulation program if needed. During follow-up, the effectiveness of SCS was assessed with regards to pain reduction and improvement of QoL. After 12-month follow-up, the study ended. Patients could then choose whether they wanted to continue using the device or request explantation. Further examinations will be performed once per year according to local protocol.

Outcome Measures and Data Collection

We conducted a feasibility pilot study with a maximum intended sample size of 10 patients with permanent implantation of a SCS device. However, an interim analysis was performed when ≥ seven participants benefited from permanent SCS device implantation at their 6-month follow-up appointment, whereafter inclusion stopped. Benefit was defined as ≥ 50% pain symptom improvement given SCS was then considered successful for endometriosis-related visceral pain. The primary outcome was pain reduction, assessed using the NRS (0-10). Secondary outcomes included changes in QoL using self-reported scores (in NRS, 0-10), the Endometriosis Health Profile-30 (EHP-30) questionnaire [22], the Patient Global Impression of Change (PGIC), the Pain Catastrophizing Scale (PCS), and use of analgesics. Changes in fatigue were measured using the Short Fatigue Questionnaire (SFQ). Finally, serious adverse events and the occurrence of overstimulation, which includes a tingling feeling in the limbs and a feeling of agitation and/or restlessness in the legs, were monitored.

Patient characteristics were extracted from the electronic patient file. Scores for worst pain, dysmenorrhea, dyspareunia, and CPP (in NRS, 0-10) were assessed at every follow-up visit and collected by the researcher from the written status of follow-up visits at the outpatient clinic of the Amsterdam UMC. Dysuria, dyschezia, and QoL were assessed at baseline and at 3-, 6-, and 12-month follow-up. Symptom scores ranged from 0 to 10, with 0 indicating absence of the symptom and 10 extreme severity. QoL also was scored from 0 to 10, wherein 0 represented the worst imaginable QoL and 10 the best imaginable QoL. Furthermore, participants reported subjective improvement (in percentages) at each visit. A set of questionnaires (EHP-30, PCS, SFQ, PGIC) and a pain diary were sent at baseline and at 3-, 6-, and 12-month follow-up. The EHP-30 questionnaire is a validated and frequently used tool to assess QoL in women diagnosed with endometriosis and can be measured in 11 different domains. With the EHP-30, low scores represent better QoL in the specific domain [23]. The SFQ is used to validate fatigue, whereby high scores indicate more fatigue. The PCS is used to assess the level of catastrophizing by patients regarding their endometriosis-associated symptoms, whereby a high score indicates high catastrophizing regarding their pain symptoms. Finally, the PGIC ranging from 1 (a lot better) to 7 (a lot worse) was used to assess whether participants considered SCS effective in the reduction of their pelvic pain symptoms.

Statistical Analysis

Data analysis was performed using SPSS Statistics (IBM version 26.0). Baseline characteristics were expressed in mean values with SD or numbers with percentages (%). The reported pain scores, QoL (both measured using NRS), the EHP-30, the PGIC questionnaire, SFQ, and PCS questionnaire were analyzed using repeated-measures analysis of variance.

RESULTS

Of 12 patients who were included, 9 participants underwent implantation of a SCS device. Three participants withdrew from study participation before SCS implantation. Nine patients started and completed the trial period, and all received permanent implantation. At the end of the 12-month follow-up, a total of 8 patients continued using the SCS device, whereas one patient requested device explantation after 12-month follow-up owing to lack of effect. There was no loss to follow-up (Fig. 1).

Baseline Characteristics

All 9 participants were diagnosed with American Society for Reproductive Medicine grade III or grade IV endometriosis. All baseline characteristics, including previous surgeries, the different types of hormonal therapy, and pain treatment before SCS implantation are listed in Table 1.

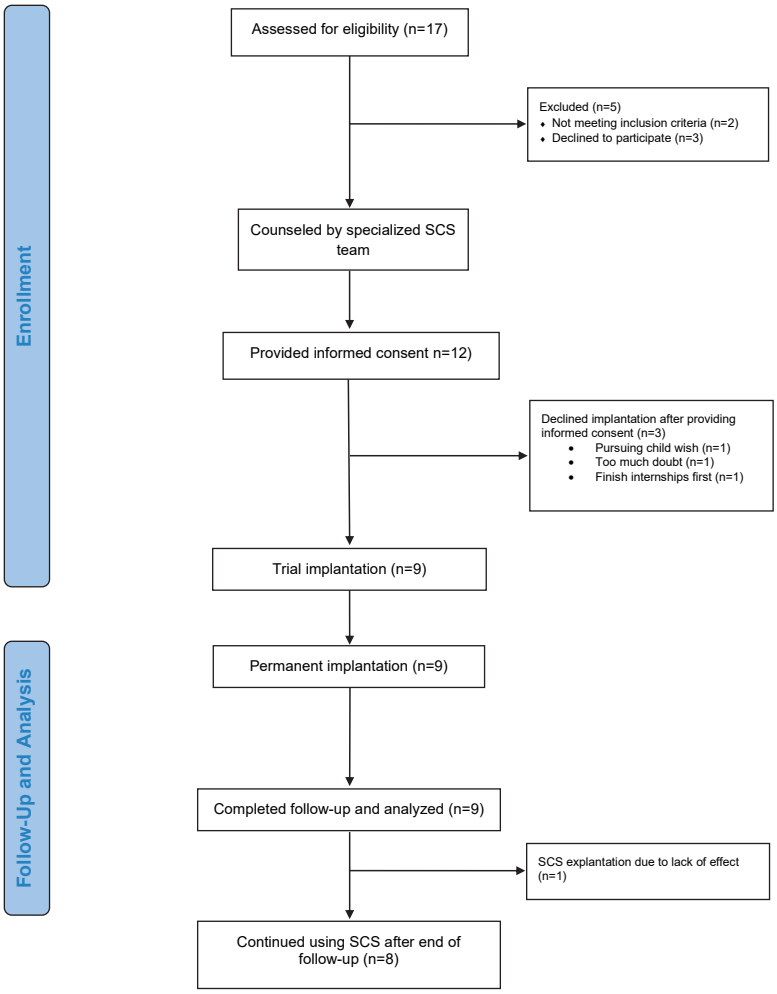

Figure 1. Flowchart of inclusion

The effect of SCS on endometriosis-related pain

For the primary outcome measure, endometriosis-related pain was studied. When comparing baseline with 12-month follow-up, significant improvement was observed in dysmenorrhea with a mean difference (MD) of 2.75 ($p = 0.025$), in chronic pelvic pain (CPP) with an MD of 3.88 ($p < 0.001$) and in dyschezia with an MD of 3.75 ($p = 0.025$). In general pain (MD 4.29, $p < 0.001$) and worst pain related to gluteal, back, vaginal, bladder or leg pain (MD 2.58, $p = 0.023$) scores, significant improvements were observed when comparing baseline with 12-month follow-up (Table 2). The course of CPP from baseline to 12-month follow-up is displayed in Figure 2. At 12-month follow-up, participants reported improvements between 50% and 100% (Table 3).

Table 1. baseline characteristics

Characteristics	Frequency (percentage)
Age at time of implantation	43.68 (10.69)[1]
BMI (kg/m^2)	28.03[1]
Previous pregnancies	
Yes	8 (88.9%)
No	1 (11.1%)
Grade of endometriosis (ASRM)	
Grade I	None
Grade II	None
Grade III	2 (22.2%)
Grade IV	7 (77.8%)
Deep endometriosis	
Yes	5 (55.6%)
No	4 (44.4%)
Location of deep endometriosis	
Bladder	1 (11.1%)
Intestines	2 (22.2%)
Vagina	1 (11.1%)
Distal ureter	None
Sacrouterine ligament	3 (33.3%)
Diaphragm	None
Abdominal Wall	1 (11.1%)
Other[2]	3 (33.3%)
Presence of adenomyosis	
Yes	3 (33.3%)
No	6 (66.7%)
Type of adenomyosis	
Focal adenomyosis	None
Anterior wall	1 (33.3%)
Posterior wall	None
Diffuse adenomyosis	2 (66.7%)
Unknown, seen with TLH	
Previous hormonal treatment	
Oral contraceptives	6 (66.7%)
Progestogens	4 (44.4%)
GnRH agonists	6 (66.7%)
IUD	1 (11.1%)
IUD combined with oral contraceptives	None
Other	1 (11.1%)
Number of gynaecological operations	
No operations	2 (22.2%)
1 operation	1 (11.1%)
2 operations	3 (33.3%)
3 operations	1 (11.1%)
>3 operations	2 (22.2%)

Table 1. baseline characteristics (*continued*)

Characteristics	Frequency (percentage)
Type of operations	
Hysterectomy	5 (55.6%)
Adhesiolysis	6 (66.7%)
Low Anterior resection	1 (11.1%)
Cystectomy	4 (44.4%)
Ovariectomy	2 (22.2%)
Tubectomy	2 (22.%)
Adnectomy	3 (33.3%)
Abdominal wall endometriosis excision	1 (11.1%)
Ureter neo-implantation	2 (22.2%)
Other[3]	3 (33.3%)
Previous anesthesiological treatment	
Paracetamol	7 (77.8%)
COX I and II inhibitors	5 (55.6%)
Anti-epileptics	7 (77.8%)
Anti-depressants	8 (88.9%)
Opioids	8 (88.9%)
TENS	8 (88.9%)
Interventional pain treatment (neurolytic blockage)[4]	2 (22.2%)

[1] means with standard deviations. [2] deep endometriosis located at the torus uteri, fornix posterior, fossa ovarica and cavum Douglasi

[3] salpingo-ovariolysis, partial sigmoid resection, bowel adhesiolysis. [4] Impar RF blockage and TAP/rectus block injection on the left (suspicion ACNES).

Table 2. Reported pain scores in NRS (scale 0-10) reported at baseline, after trial period, at 1 month follow-up, at 3 month follow-up, at 6 month follow-up and 12 month follow-up.

Reported symptoms (follow-up periods)	Pain scores Mean (SD)	Mean difference[1]	P-value[1]
General pain scores [2]			
Baseline	6.77 (0.29)	3.96	0.036
3 month follow-up	2.81 (0.65)	3.82	0.002
6 month follow-up	2.96 (0.32)	4.29	<0.001
12 month follow-up	2.48 (0.20)		
Worst pain scores [3]			
Baseline	5.33 (0.29)	4.45	0.004
1 month follow-up	0.88 (0.43)	4.83	0.003
3 month follow-up	0.50 (0.29)	3.83	0.014
6 month follow-up	1.50 (0.87)	2.58	0.023
12 month follow-up	2.75 (0.72)		
Dysmenorrhea			
Baseline	7.25 (0.48)	4.12	<0.001
1 month follow-up	3.13 (0.52)	3.75	0.017
3 month follow-up	3.50 (1.24)	2.63	0.171
6 month follow-up	4.63 (1.93)	2.75	0.025
12 month follow-up	4.50 (1.02)		

Table 2. Reported pain scores in NRS (scale 0-10) reported at baseline, after trial period, at 1 month follow-up, at 3 month follow-up, at 6 month follow-up and 12 month follow-up. (*continued*)

Reported symptoms (follow-up periods)	Pain scores Mean (SD)	Mean difference[1]	P-value[1]
Dyspareunia			
Baseline	8.50 (0.50)	5.50	0.361
1 month follow-up	3.00 (3.00)	5.00	0.430
3 month follow-up	3.50 (3.50)	5.50	0.361
6 month follow-up	3.00 (3.00)	4.75	0.465
12 month follow-up	3.75 (3.75)		
CPP			
Baseline	6.25 (0.37)	3.00	0.001
After trial period	3.25 (0.62)	4.19	<0.001
1 month follow-up	2.06 (0.36)	3.56	<0.001
3 month follow-up	2.69 (0.38)	3.81	<0.001
6 month follow-up	2.44 (0.38)	3.88	<0.001
12 month follow-up	2.38 (0.71)		
Dysuria			
Baseline	4.33 (0.67)	4.33	0.023
3 month follow-up	0.00 (0.00)	4.00	0.020
6 month follow-up	0.33 (0.33)	3.33	0.063
12 month follow-up	1.00 (1.00)		
Dyschezia			
Baseline	5.86 (0.80)	3.57	0.007
3 month follow-up	2.29 (0.84)	5.57	<0.001
6 month follow-up	0.29 (0.29)	3.75	0.025
12 month follow-up	2.11 (1.01)		

[1] Significance measured by comparing baseline to the different follow-up moments. [2] Measured using a pain diary where patients reported general pain scores thrice daily, over a period of three days. Average scores were calculated per day and per follow-up period at baseline, 3 month, 6 month and 12 month follow-up. [3] Worst pain included butt pain, back pain, vaginal pain, bladder pain and leg pain. Some participants reported more than one location where their pain was the worst, but lack of data made it not possible to analyze the second worst pain scores.

Table 3. Reported improvement of pain by participants during the trial period, at 1-month, 3-month, 6-month and 12-month follow-up.

Participant	Self-reported percentage of improvement				
	Trial period	**1-month FU**	**3-month FU**	**6-month FU**	**12-month FU**
1	60-70%	60-70%	50%	80%	70%
2	Stomach: 28% Back: 64%	30-40%	Unable to score	0-10%	Explantation
3	60%	50-60%	Unable to score	80-85%	85-90%
4	90%	A little more than 50%	At least 50%	80%	At least 60%
5	Unable to score	50%	20%	20%	50%
6	At least 50%	At least 60%	60-70%	60%	70%
7	50-60%	90%	90%	90%	85%

Table 3. Reported improvement of pain by participants during the trial period, at 1-month, 3-month, 6-month and 12-month follow-up. (*continued*)

Participant	Self-reported percentage of improvement				
	Trial period	**1-month FU**	**3-month FU**	**6-month FU**	**12-month FU**
8	70%	75-80%	75-80%	75-80%	75-80%
9	100%	90%	90%	90-100%	90-100%

The effect of SCS on QoL

As a secondary outcome, QoL was evaluated. Significant improvement was observed in self-reported QoL scores when comparing baseline with 12-month follow-up, with an MD of 1.84 (p = 0.040). Furthermore, significant improvements were observed in the EHP-30 core domains of Pain (MD 24.62, p = 0.005), Control and Powerlessness (MD 31.95, p = 0.019), Social Support (MD 21.88, p = 0.006), and Self Image (MD 30.56, p = 0.010) when comparing baseline and 12-month follow-up (Table 4).

The effect of SCS on different measurement tools

A significant improvement in PGIC was seen, when participants reported an average score of 4.4 (between "similar" and "a little worse") at baseline vs 1.7 (much better) at 12-month follow-up (range P = 0.002 - 0.003). The other questionnaires that were distributed at the different follow-up moments showed no significant improvements (Table 5).

Table 4. Quality of Life (QoL) reported at baseline, at 3 month follow-up, at 6 month follow-up and at 12 month follow-up. QoL was measured both by self-reported scores, in NRS (scale 0-10) and the EHP-30 questionnaire.

Self-reported QoL scores	**QoL scores (mean (SD))**	**Mean difference[1]**	**P-value[1]**
Quality of Life (QoL) in			
NRS	5.19 (0.66)	2.31	0.022
Baseline	7.50 (0.28)	2.31	0.018
3 month follow-up	7.50 (0.30)	1.84	0.040
6 month follow-up	7.03 (0.36)		
12 month follow-up			
Core domains EHP-30	QoL scores (mean (SD))		P-value[1]
Pain			
Baseline	88.64 (5.01)	31.06	0.023
3 month follow-up	57.58 (7.13)	26.14	0.004
6 month follow-up	62.50 (3.46)	24.62	0.005
12 month follow-up	64.02 (5.06)		
Control and Powerless-			
ness	75.00 (7.68)	33.33	0.023
Baseline	41.67 (4.93)	32.64	0.015
3 month follow-up	42.36 (3.94)	31.95	0.019
6 month follow-up	43.06 (4.65)		
12 month follow-up			

Table 4. Quality of Life (QoL) reported at baseline, at 3 month follow-up, at 6 month follow-up and at 12 month follow-up. QoL was measured both by self-reported scores, in NRS (scale 0-10) and the EHP-30 questionnaire. (*continued*)

Self-reported QoL scores	**QoL scores (mean (SD))**	**Mean difference[1]**	**P-value[1]**
Emotional Wellbeing			
Baseline	53.47 (9.71)	15.97	0.067
3 month follow-up	37.50 (4.30)	14.58	0.084
6 month follow-up	38.89 (5.01)	14.58	0.115
12 month follow-up	38.89 (5.66)		
Social Support			
Baseline	80.21 (10.63)	29.17	<0.001
3 month follow-up	51.04 (7.11)	31.25	0.009
6 month follow-up	48.96 (6.34)	21.88	0.006
12 month follow-up	58.33 (9.08)		
Self-Image			
Baseline	83.33 (9.62)	36.11	0.007
3 month follow-up	47.22 (9.04)	37.50	<0.001
6 month follow-up	45.83 (7.06)	30.56	0.010
12 month follow-up	52.78 (9.78)		
Modular domains EHP-30	QoL scores (mean (SD))	Mean difference[1]	P-value*
Work Life			
Baseline	67.50 (12.50)	25.00	0.242
3 month follow-up	42.50 (2.50)	27.50	0.170
6 month follow-up	40.00 (5.00)	35.00	0.330
12 month follow-up	32.50 (7.50)		
Children			
Baseline	56.25 (7.03)	27.08	0.027
3 month follow-up	29.17 (4.17)	25.00	0.049
6 month follow-up	31.25 (4.27)	20.83	0.080
12 month follow-up	35.42 (3.84)		
Sexual Intercourse			
Baseline	56.67 (12.76)	9.17	0.520
3 month follow-up	47.50 (17.92)	14.17	0.323
6 month follow-up	42.50 (16.47)	5.83	0.629
12 month follow-up	50.83 (13.26)		
Medical Profession	*Unable to calculate due to lack of data*		
Treatment	*Unable to calculate due to lack of data*		
Infertility	*Unable to calculate due to lack of data*		

[1] Significance measured by comparing baseline to the different follow-up moments

Table 5. Questionnaires

Questionnaire scores	Pain scores (mean (SD))	Mean difference[1]	P-value[1]
PGIC[2] questionnaire			
Baseline	4.43 (0.37)	2.57	0.002
3 month follow-up	1.86 (0.26)	2.57	0.003
6 month follow-up	1.86 (0.26)	2.71	0.002
12 month follow-up	1.71 (0.29)		
PCS[3] questionnaire			
Hopelessness			
Baseline	9.60 (3.80)	7.80	0.118
3 month follow-up	1.80 (0.37)	7.20	0.156
6 month follow-up	2.40 (0.68)	6.40	0.209
12 month follow-up	3.20 (1.02)		
Rumination			
Baseline	7.00 (2.61)	4.00	0.220
3 month follow-up	3.00 (0.95)	4.80	0.201
6 month follow-up	2.20 (0.97)	4.60	0.199
12 month follow-up	2.40 (0.87)		
Magnification			
Baseline	3.60 (2.29)	3.00	0.255
3 month follow-up	0.60 (0.25)	3.00	0.189
6 month follow-up	0.60 (0.40)	2.60	0.217
12 month follow-up	1.00 (0.55)		
SFQ[4]			
Baseline	17.67 (1.80)	1.83	0.202
3 month follow-up	15.83 (1.52)	1.83	0.470
6 month follow-up	15.83 (2.50)	-1.00	0.530
12 month follow-up	18.67 (2.14)		

[1] Significance measured by comparing baseline to the different follow-up moments. [2] PGIC: Patients Global Impression of Change questionnaire. [3] PCS: Pain Catastrophing Scale. [4] SFQ: Shortened Fatigue Questionnaire

The effect of SCS on medication use

At baseline, all participants used one or multiple forms of pain medication, which included paracetamol, nonsteroidal anti-inflammatory drugs, tramadol, opioids, tricyclic antidepressants, and Lyrica. At 12-month follow-up, 4 participants were able to reduce their pain medication, and 4 participants were able to discontinue all analgesics. One participant who requested explantation experienced no change in analgesics use (Table 6).

Table 6. Medication use by all participants, at baseline compared to 12-month follow-up.

Participant	Medication at baseline	Medication at 12-month follow-up
1	Fentanyl patch 12mcg one per 3 days Amitriptyline 30 mg once daily	Amitriptyline 30 mg ante noctum
2	Celecoxib 200mg twice daily Tramadol 50mg twice daily	Celecoxib 200mg twice daily Tramadol 50mg twice daily
3	Tramadol 50mg once to three times daily Temazepam 20mg once daily Pregabaline 75mg twice daily	No more pain medication needed.
4	Oxycodon 5mg once to twice daily	No more pain medication needed.
5	Gabapentine 300mg in the evening, 100mg in the afternoon Oxycodon 25mg twice daily Oxycodon short-acting 5mg, one to six times daily if needed Paracetamol 1000mg three times daily	Oxycodon 10mg twice daily Oxycodon short-acting 5mg, once daily
6	Paracetamol 1000mg three times daily Tramadol 50mg three times daily if needed	No more pain medication needed.
7	Paracetamol 1000mg four times daily	No more pain medication needed.
8	Buprenorfin patch 10mcg/hour, one per week Amitriptyline 10mg three times daily Pregabalin 75mg two times daily	Buprenorfin patch 5mcg/hour, one per week Pregabalin 75mg two times daily
9	Tramadol 50mg once daily	Paracetamol 1000mg four times daily if necessary.

Side effects and adverse events

No serious adverse events related to the SCS device were reported. Two participants experienced overstimulation with heavy legs or stiff muscles which quickly disappeared after reprogramming. One participant needed lead replacement owing to malfunction at 1-month follow-up. Three participants experienced an uncomfortable feeling around the lead anchors, mostly because the anchors lay more superficially after weight loss. One participant underwent anchor revision because of this uncomfortable feeling. One participant experienced heating of the IPG during charging and small shocks at the IPG site leading to its replacement, when it was decided to implant a nonrechargeable IPG (Table 7).

Table 7. Side Effects and Adverse Events Associated With the SCS Device.

No. of participants	Side effects	Consequences
1	Lack of efficacy	Explantation
1	Lead malfunction	Lead replacement
1	Uncomfortable heat IPG when charging and small shocks in area of IPG	Revision IPG
4	Lead anchors more superficial after weight loss (n=3), skin bump at anchor lead (n=1)	Anchor revision (n=1)
2	Overstimulation (stiff muscles, heavy legs)	Adjustment of program (n=2)

DISCUSSION

On the basis of our results, SCS appears a feasible treatment for intractable, endometriosis-related visceral pain. We found improved scores in dysmenorrhea, CPP, dyschezia, general and worst pain scores when comparing baseline and 12-month follow-up. Furthermore, significant improvement in self-reported QoL and in all but one core domains of the EHP-30 was observed when comparing baseline with 12-month follow-up. Eight participants continued using the device after 12 months. All participants but one were able to reduce or even discontinue their analgesics. Nonetheless, given this was a feasibility pilot study without a calculated sample size, the results should be interpreted with caution because the positive effects cannot be attributed with full certainty to SCS.

Strengths and limitations

Our study has several strengths. First, feasibility and efficacy of SCS for endometriosis were studied from a holistic approach that not only focused on the effect of SCS on pain reduction but also on patient-reported outcomes such as QoL. Second, participants frequently visited the hospital for follow-ups according to local protocol to meticulously monitor the effect of SCS and adjust the device settings if necessary. Finally, a dedicated researcher was present during trial and permanent implantation and during all follow-up moments for each participant. Our study also has several limitations. First, we were unable to perform a sample size calculation owing to lack of data from previous studies. Therefore, the positive effects cannot be attributed with full certainty to SCS. Furthermore, the small sample size led to an inability to correct our multiple comparisons. Therefore, the results can be interpreted on effect sizes and measures of precision, and seen as explanatory results of null-hypothesis testing. Given all participants received SCS and this study was neither blinded nor randomized, we were unable to match the results to a control group to eliminate the placebo effect. A previous systematic review with meta-analysis found that, among patients with CPP syndrome, a considerable placebo effect on subjective parameters, including pain and QoL, was reported [24]. This underlines the importance of performing studies with a randomized, preferably blinded, design in the future.

Comparison with previous literature

We found that SCS was a feasible option for treatment of the endometriosis-related symptoms of dysmenorrhea, dyschezia, and CPP. Until now, studies on the effect of SCS specifically for endometriosis-related visceral pain were lacking. There are several studies applying different forms of neuromodulation for CPP but not specifically caused by endometriosis that found similar favorable results that accord with our study [25-35]. More recently, however, da Silva Freitas et al applied dorsal-root ganglion stimulation for CPP secondary to endometriosis, when they implanted the device bilaterally in L1 and S2. The authors found similar reductions in CPP and significant improvements in pain medication use, with four of their participants being able to discontinue opioids use entirely [36]. The effectiveness of various neuromodulation modalities targeting different levels of the spinal cord highlights the complexity of pelvic innervation, which includes responsibility of both somatic and sympathetic fibers for pain transmission. However, with placement in L1, this too covers the nn Splanchnici, which are responsible for innervation of the viscera [35]. This suggests that to optimally treat endometriosis-related pain symptoms, a multimodal approach might be required. It could combine stimulation at different levels of the spinal cord and different types of neuromodulation. Future studies should aim to identify the most effective combinations and stimulation sites to maximize therapeutic outcomes.

We found improved QoL, both in self-reported scores and in the EHP-30 questionnaire. Furthermore, our participants reported being able to participate again in social activities and roles, to be more active, and to resume their sport activities after being unable to do so for years owing to their debilitating pain. Similarly, Lavonius et al provided sacral neuromodulation for endometriosis and found reduced pain symptoms that enabled their participants to work, have a social life, and travel, ultimately leading to a significant improvement in QoL [27]. Previous studies suggested a strong association between pain and QoL, in which patients with endometriosis reported worse physical and mental QoL than those of healthy women. Furthermore, pain cognition negatively affected QoL, independent of pain intensity [37, 38]. Therefore, not just optimization of pain management but also mental guidance that can provide tools for pain acceptance might be important owing to its positive impact on QoL, work-, and social life [39]. This has led to the call among health care providers to evaluate new treatment methods from a holistic perspective, focusing on more than just pain reduction. The patients' needs are evaluated across a range of health domains by establishing a minimal clinically important difference to reflect improvements in health domains that patients consider relevant [40]. This way, efficacy of treatment can be evaluated in a multifaceted manner rather than just regarding the reduction of pain symptoms. A distinction can then be drawn between patients who experience significant pain relief but remain limited in their ability to participate in daily life, and those with suboptimal pain relief but can fully engage in society again. We emphasize the importance of evaluating all health aspects leading to better societal par-

ticipation, not just symptom reduction itself, when studying this new treatment method for intractable endometriosis [40].

CONCLUSION

Our prospective pilot study suggests that SCS is feasible and might be beneficial for women with intractable, endometriosis-related visceral pain. During a 12-month follow-up period, improvement was observed in endometriosis-related symptoms, causing 5 of 9 participants to be able to discontinue all pain medication. Moreover, significant improvement in QoL was seen. One participant requested explantation at 12-month follow-up owing to lack of effect. Side effects occurred in 6 participants but were neither more severe nor occurred more frequently than in other studies. This could suggest that SCS is a safe treatment option for intractable, endometriosis-related visceral pain. We emphasize the need to further broaden the knowledge on the appliance of SCS for endometriosis by performing a high quality, multicenter randomized controlled trial with a calculated sample size and holistic outcome measures, including a cost-effectiveness analysis.

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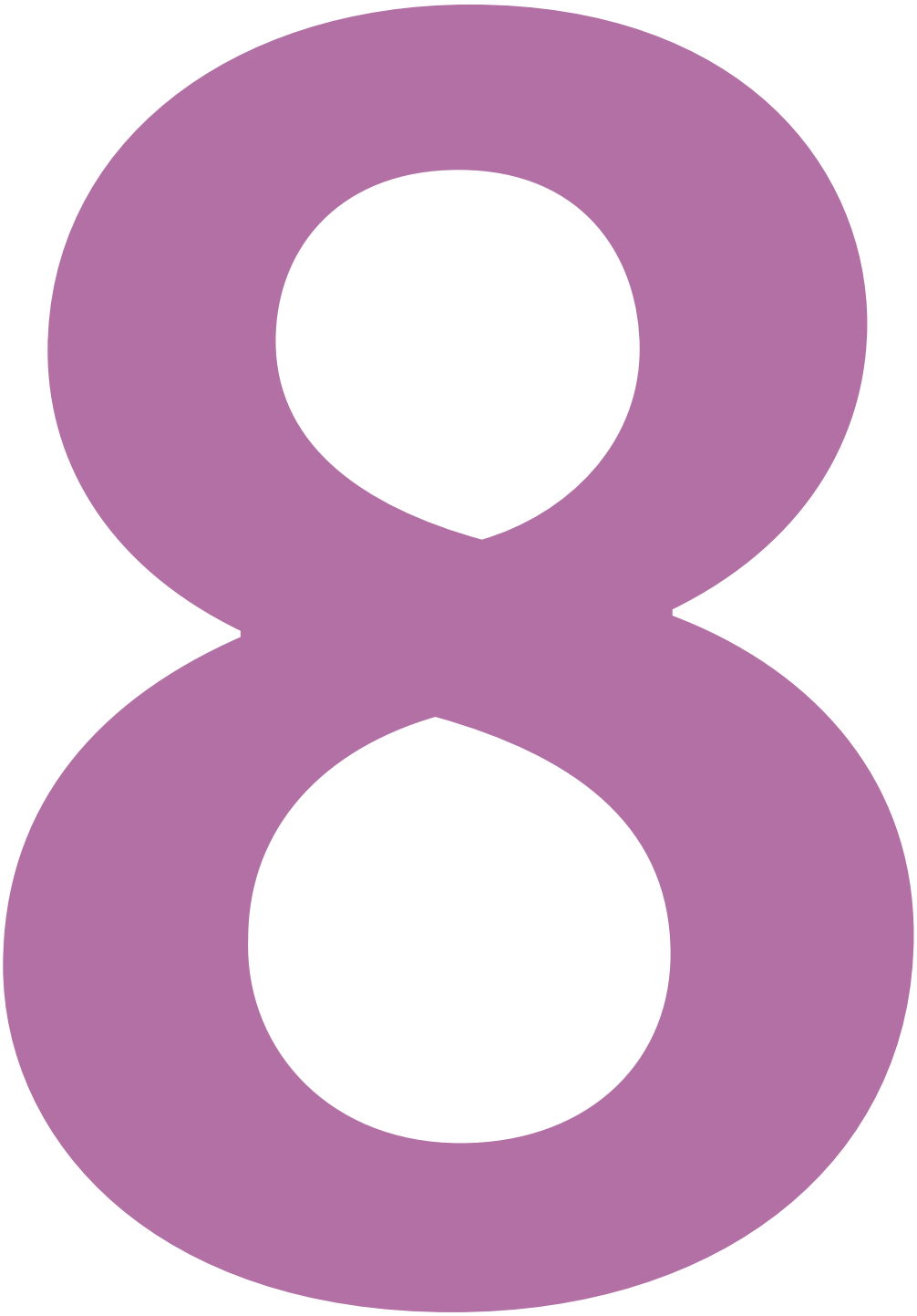
Part III

Dietary interventions in the chronic endometriosis patient





Chapter 8

A better quality of life could be achieved by applying the endometriosis diet: a cross-sectional study in Dutch endometriosis patients

Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Velja Mijatovic

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ABSTRACT

Research question: Does the endometriosis diet positively affect quality of life (QoL) in women diagnosed with endometriosis?

Design: A cross-sectional study was performed, recruiting women using the website and online peer platforms from the Dutch Endometriosis Society. In total, 211 women with a self-reported diagnosis of endometriosis were included in the study. They completed a questionnaire on the six QoL domains based on the conversation tool 'My Positive Health'. Women who adhered to the endometriosis diet were compared with women who did not. A distinction was made between strict (score ≥8 on a scale of 0–10) and less strict adherence to the diet.

Results: A significantly higher score was seen in all six QoL domains in women who adhered to the endometriosis diet (n = 90) compared with women who did not (n = 121) (range $P < 0.001$ to $P = 0.043$). Furthermore, women with strict adherence (n = 48) compared to less strict adherence (n = 42) reported significantly higher scores in all six QoL domains (range $P = 0.005$ to 0.05). Women diagnosed with endometriosis more than 10 years ago (n = 13) adhered to the endometriosis diet significantly less often than women that were diagnosed more recently (n = 163; range $P = 0.005$ to 0.046).

Conclusion: The endometriosis diet was associated with a better QoL in Dutch women with endometriosis. Strict adherence showed higher QoL scores compared with less strict adherence. Therefore, more research is needed to clarify the mechanism of this beneficial effect and to identify facilitators and barriers to dietary adjustments in patients with endometriosis.

INTRODUCTION

Endometriosis is a chronic condition, affecting up to 10% of women of reproductive age worldwide [1,2]. It is associated with cyclical symptoms such as dysmenorrhea, dyschezia and dysuria and non-cyclical symptoms such as deep dyspareunia, chronic pelvic pain and infertility [1]. Furthermore, less specific symptoms can occur such as bloating, back pain and fatigue, which have an overlap with irritable bowel syndrome [1,3]. The symptoms can have a negative effect on several aspects of a patient's quality of life (QoL) and psychosocial functioning [4]. Previous cross-sectional research by these authors found that 51% of participants reported a negative effect of endometriosis on their work and career, 50% on their personal relationships and 16% on their education [4]. Additionally, endometriosis can negatively impact the patient's self-image, and contribute to feelings of powerlessness and frustration [5].

There is no definitive cure for endometriosis, therefore providing adequate treatment can be challenging [6]. Treatment of endometriosis is based on three important principles: the reduction of pain symptoms, improvement in QoL, and prevention of disease progression and/or recurrence [1,6]. Treatment usually includes adequate pain management, hormonal suppression therapy and/or surgery. In addition, women suffering from endometriosis-related infertility can undergo treatment with assisted reproductive techniques [1]. However, these treatment options are not always sufficient to reduce symptoms and can fail to optimize a patient's QoL. Also, a proportion of women experience side effects of medical treatment that may lower long-term compliance. Therefore, women with endometriosis are often searching for ways to increase their self-sufficiency. Alternative treatment methods, such as dietary interventions, are gaining interest and have been increasingly researched in recent years [7]. It is postulated that certain dietary supplements might have a synergistic effect, functioning as an anti-inflammatory, antioxidant, anti-proliferative and immune-modulatory agent. This can result in the suppression of endometriosis and its associated symptoms [7,8]. Several dietary interventions have been shown to be efficient in the reduction of endometriosis symptoms such as the low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet, the endometriosis diet, or a gluten- or lactose free diet [3,9,10]. In 2020, a large systematic review by Nap et al. found that both the addition (such as omega-3 and -6, several vitamins and minerals) and the avoidance of certain nutrients (gluten, soy) was associated with a reduction of endometriosis-related symptoms [7]. These findings were confirmed by the systematic review by Yalcin Bahat et al. (2022) [8]. In addition, Marziali et al. (2012) found that adherence to a gluten-free diet significantly improved QoL [10]. Finally, by adhering to a dietary intervention, with the aim of reducing symptoms, women can feel more self-sufficient and in control of their symptoms, resulting in a significantly higher reported QoL [11,12].

A diet frequently applied by Dutch women experiencing endometriosis-related pain is the endometriosis diet [13]. This diet was developed by women diagnosed with endometriosis and is based on the avoidance of nutrients (e.g. red meat, caffeine, sugar) they noticed provoked or aggravated their symptoms. However, several variations of the diet exist and there are currently no guidelines available on its exact implementation. In this study, the objective was to determine the impact of the endometriosis diet, as recommended by the Dutch Endometriosis Society and applied by Dutch women suffering from endometriosis, on their QoL.

METHODS AND MATERIALS

Study design

A cross-sectional study was performed that included women with a self-reported diagnosis of endometriosis. Women currently adhering to the endometriosis diet were compared to women not adhering to the endometriosis diet. Women based the diet on two sources, both recommended by the Dutch Endometriosis Society (Endometriose Stichting; the Dutch patient organization): www.endometriosedieet.nl and www.endometriosetelijf.nl. The study was initiated at the Hague University of Applied Sciences. Because there was no Medical Ethics Committee at the Hague University at the start of this study, no ethical approval could be granted.

Study population

Women were recruited from the website of the Dutch Endometriosis Society (www.endometriose.nl) and online peer platforms connected to the Dutch Endometriosis Society [14]. Women were included in the study if they were 18 years and older. Non-Dutch speaking women were excluded from participation.

Study procedure

After women confirmed their willingness to participate in the study, they were asked to complete a digital questionnaire that was distributed using the online survey program GoogleForms®, part of Google Workspace®. Basic demographics, specifics on the use of the endometriosis diet (including reasons to start or discontinue the diet and difficulties encountered when adhering to it) and the participant's QoL were assessed. Furthermore, women were asked how strict their adherence was to the endometriosis diet. They could rate themselves between 'no strict adherence at all' ('0') and 'very strict adherence' ('10'). An 11-point rating scale is considered an appropriate and validated response scale option; it is more normally distributed than a shorter response scale. Participants can discriminate well between the meanings behind 0 and 10 [15].

Based on the median, a cut-off value of 8 was used to distinguish between strict and non-strict adherence to the diet. Finally, to assess QoL, the conversation tool 'My Positive Health' was incorporated into the questionnaire, consisting of 42 questions divided into six domains: physical functioning, psychological functioning, spiritual functioning, quality of life, social participation and daily functioning [16-18]. Women were asked to score these six domains of their QoL, and rate them on an 11-point Likert scale. The detailed questionnaire can be found in the Supplementary Appendix.

The endometriosis diet

The endometriosis diet is based on patient experiences, with a considerable variation in how women apply it. Avoidance of nutrients considered by the researchers as part of the endometriosis diet, was mentioned at the beginning of the questionnaire. If women felt that this specific explanation of the endometriosis diet fitted their diet, they were prompted to complete the questionnaire. The nutrients avoided as part of the endometriosis diet are shown in Table 1.

Table 1. Avoidance of nutrients considered part of the endometriosis diet.

Nutrient group	Examples
Red meat	Beef, pork, lamb, mutton, veal, horse, liver
Gluten	(Khorasan) wheat, rye, spelt, barley
Lactose	A sugar found in e.g. milk, cheese spreads, whey-based soft drinks, ice cream
Sugars	All added sugars. Refined sugars (cane sugar, caster sugar), natural sugars (honey, palm sugar) and sweeteners (aspartame, polyols)
Nutrients high in estrogen	Soy (soymilk, tofu, soya sprout, miso, tempeh, soy sauce, natto), linseed, sesame seeds, black beans

Outcome measures

The primary outcome focused on the effect of the endometriosis diet on women's QoL. Secondary outcomes focused on the influence of strict or less strict adherence to the endometriosis diet on QoL, the influence of time since diagnosis of endometriosis on adherence to the diet, and reasons to discontinue the endometriosis diet.

Statistical analysis

Data analysis was performed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics are expressed as mean values with SD or numbers with percentages. Differences in baseline characteristics were calculated using the chi-squared test. The difference between the two groups (diet versus no diet) was calculated using a linear regression. To differentiate between once adhering, never adhering and currently adhering to the endometriosis diet, dummy variables were created and analyzed using a linear regression. To analyse the duration of diagnosis and the efficacy

of the endometriosis diet, a logistic regression was used. Data were corrected for the following confounders: the participant's age, severity (grade) of endometriosis and duration of diet adherence. A P-value of ≤0.05 was considered statistically significant.

RESULTS

Between 9 April and 22 April 2019, a total of 212 questionnaires were collected. However, one participant completed the questionnaire twice and so a total of 211 participants were included in the study. Participant recruitment is shown in Figure 1. Ninety out of 211 participants adhered to the endometriosis diet. Of the 121 participants that currently did not adhere to the endometriosis diet, 27 women previously had done. No statistically significant differences were seen in baseline characteristics of the diet users versus the non-users. All patient characteristics are presented in Table 2.

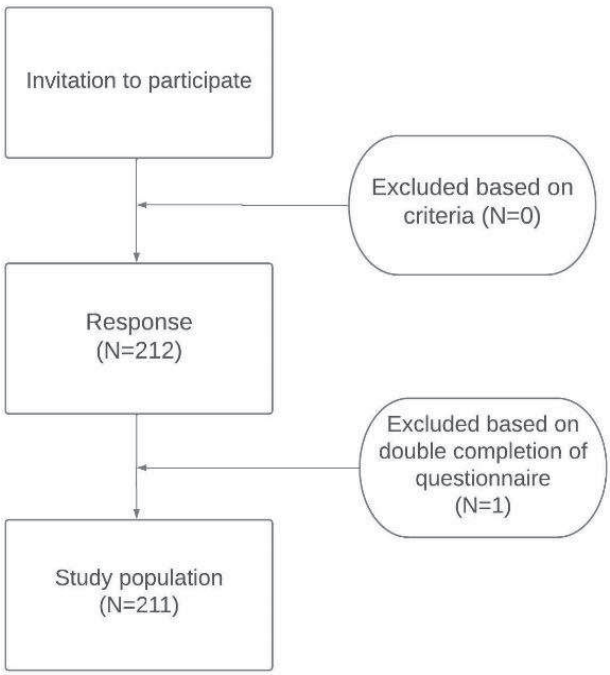

Figure 1. Patient recruitment

Table 2. Baseline characteristics in endometriosis diet users compared with non-users.

Patient characteristics	Endometriosis diet (n=90)	No endometriosis diet (n=121)	Total (n=211)	Significance P-value
Age in years, mean (SD)	35.9 (6.88)	35.8 (7.64)	35.9 (7.31)	0.90
Adherence to diet (score 1-10)				
Score 1-7	42 (46.7)	-	-	
Score 8 – 10	48 (53.3)	-	-	
Previous adherence to the diet	0 (0)	27 (22.3)	27 (12.8)	
Years since diagnosis				
0-1 Years	16 (17.8)	20 (16.6)	36 (17.0)	0.067
1-5 Years	34 (37.8)	42 (34.7)	76 (36.0)	
5-10 Years	27 (30)	24 (19.8)	51 (24.2)	
>10 Years	13 (14.4)	35 (28.9)	48 (22.8)	
Grade of Endometriosis				
ASRM grade I	6 (6.7)	4 (3.3)	10 (4.7)	0.79
ASRM grade II	3 (3.3)	3 (2.5)	6 (2.9)	
ASRM grade III	10 (11.1)	14 (11.6)	24 (11.4)	
ASRM grade IV	41 (45.6)	54 (44.6)	95 (45.0)	
Unknown	30 (33.3)	46 (38.0)	76 (36.0)	

Data are presented as n(%) unless otherwise stated.

Participants were asked to score the six domains of their QoL. Participants who applied the endometriosis diet scored significantly higher on all QoL domains (range $P < 0.001$ to $P = 0.043$) than participants who did not apply the diet (Table 3).

Table 3. Scores in the six domains of quality of life (QoL) for endometriosis users compared with non-users.

Domains of Quality of Life	Mean scores in the six domains of QoL		Average difference (diet versus no diet) with 95% confidence interval	Significance P-value[1]
	Endometriosis diet (n=90)	No diet (n=121)		
Physical functioning	6.33	5.27	1.06 (0.60 to 1.53)	0.000
Psychological functioning	7.36	6.74	0.63 (0.27 to 0.98)	0.001
Spiritual functioning	7.68	7.14	0.55 (0.15 to 0.94)	0.007
Quality of life	7.47	7.07	0.40 (0.01 to 0.78)	0.043
Social participation	8.29	7.63	0.66 (0.25 to 1.06)	0.002
Daily functioning	8.11	7.42	0.70 (0.30 to 1.09)	0.001

Table 3. Scores in the six domains of quality of life (QoL) for endometriosis users compared with non-users.

Domains of Quality of Life	Mean scores in the six domains of QoL		Average difference (diet versus no diet) with 95% confidence interval	Significance P-value[1]
	Endometriosis diet (n=90)	No diet (n=121)		
Physical functioning	6.33	5.27	1.06 (0.60 to 1.53)	0.000
Psychological functioning	7.36	6.74	0.63 (0.27 to 0.98)	0.001
Spiritual functioning	7.68	7.14	0.55 (0.15 to 0.94)	0.007
Quality of life	7.47	7.07	0.40 (0.01 to 0.78)	0.043
Social participation	8.29	7.63	0.66 (0.25 to 1.06)	0.002
Daily functioning	8.11	7.42	0.70 (0.30 to 1.09)	0.001

[1] calculated using linear regression. Scale 0-10.

Women once adhering to the diet but that had discontinued it previously, and women currently adhering to the diet, were compared to women who never adhered to the endometriosis diet. Only women currently adhering to the diet reported significantly higher scores in the six QoL domains (range $P < 0.000$ to $P = 0.040$), compared to women that had never used the diet. There was no significant difference between women once adhering to the diet and women that had never adhered to the diet (Table 4).

Table 4. Scores in the six domains of quality of life (QoL) for women once adhering to the diet (n=27) and women currently adhering to the endometriosis diet (n=90) compared to women never adhering to the diet (n=94).

Domains of Quality of Life	Average difference[1]		95% confidence interval (lower bound – upper bound)		Significance P-value	
	Never diet[2] versus once diet	Never diet[2] versus now diet	Never diet[2] versus once diet	Never diet[2] versus now diet	Never diet[2] versus once diet	Never diet[2] versus now diet
Physical functioning	0.20	1.11	-0.53 to 0.93	0.62 to 1.60	0.59	0.000
Psychological functioning	0.13	0.65	-0.44 to 0.69	0.27 to 1.03	0.66	0.001
Spiritual functioning	0.31	0.61	-0.31 to 0.92	0.20 to 1.03	0.33	0.004
Quality of life	0.16	0.43	-0.44 to 0.76	0.03 to 0.84	0.60	0.040
Social participation	-0.18	0.62	-0.82 to 0.47	0.18 to 1.05	0.59	0.005
Daily functioning	-0.34	0.62	-0.95 to 0.28	0.20 to 1.03	0.28	0.004

[1] scale 0-10. [2] Reference value. All groups were compared to this reference value.

Participants with strict adherence to the diet (based on the median value with a cut-off score ≥8) reported a significantly higher score in all six domains of their QoL (range P = 0.005 to 0.050) compared to participants with less strict adherence to the diet (Table 5).

Table 5. Scores in the six domains of quality of life (QoL) in women with strict adherence to the diet compared to no strict adherence.

	Mean scores in the six domains of QoL		**Average difference[2] (strict[1] versus no strict adherence) with 95% confidence interval**	**Significance** P-value
	Strict adherence (n=48)	**No strict adherence (n=42)**		
Physical functioning	6.63	5.99	0.71 (0.02 to 1.40)	0.044
Psychological functioning	7.62	7.06	0.59 (0.10 to 1.08)	0.019
Spiritual functioning	7.93	7.39	0.64 (0.11 to 1.17)	0.018
Quality of life	7.76	7.13	0.72 (0.19 to 1.25)	0.009
Social participation	8.60	7.93	0.77 (0.24 to 1.29)	0.005
Daily functioning	8.39	7.79	0.55 (0.00 to 1.10)	0.050

[1] Median score of strictness ≥8 (scale 0-10). [2] Calculated using a linear regression. Scale 0-10.

Compared to women that were diagnosed with endometriosis more than 10 years ago, women that were diagnosed less than a year ago (P = 0.046), 1.1 to 5 years (P = 0.025) or 5.1 to 10 years ago (P = 0.005) adhered to the endometriosis diet significantly more often (Table 6).

Table 6. Comparison of number of women adhering to the endometriosis diet according to time since diagnosis.

Years since diagnosis	**Average difference (number of women adhering to the diet and years since diagnosis)**	**95% confidence interval (lower bound – upper bound)**	**Significance P-value**
0-1 years (n=36)	1.06	1.02 to 8.17	0.046
1-5 years (n=76)	0.98	1.13 to 6.22	0.025
5-10 years (n=51)	1.24	1.44 to 8.28	0.005
>10 years (n=48)[1]	1.00	-	-

[1] Reference value. All time intervals were compared to the reference value.

Finally, relevant results were found from the open-ended questions. When asking participants that did not adhere to the endometriosis diet why they did not, they most frequently reported that they were unfamiliar with the diet (39%) or that the complexity (31%) played an important role in not implementing the endometriosis diet (Figure 2).

Participants that had adhered to the diet in the past often discontinued the diet because they experienced no positive results (56%) or found it too complex to use (22%) (Figure 3).

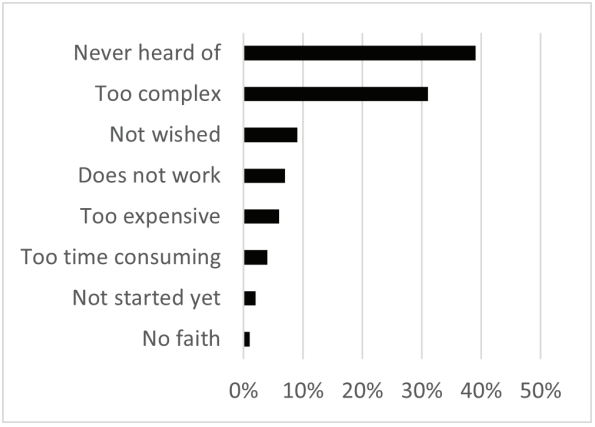

Figure 2. Reasons not to adhere to the endometriosis diet (n=121)

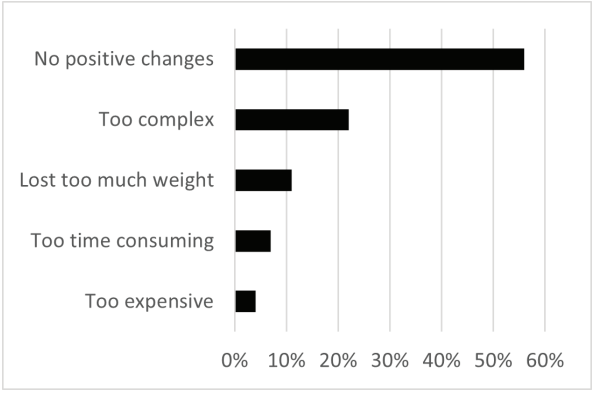

Figure 3. Reasons for discontinuing the endometriosis diet. Reported by 27 participants who had previously adhered to the diet but did not currently adhere to it.

DISCUSSION

This study provides an assessment of the impact of the endometriosis diet on QoL in Dutch women with endometriosis. It was found that using the endometriosis diet as a self-management strategy had a beneficial effect on the QoL in women diagnosed with endometriosis. This positive effect was even stronger when there was strict adherence to the diet. This is in line with the finding by Marziali et al. (2012) that the use of a gluten-free diet in women with endometriosis resulted in significantly higher scores in all QoL domains [10]. The effectiveness of both diets can possibly be explained by the fact that they

influence endometriosis by causing an anti-inflammatory, antioxidant and anti-estrogenic effect. This is especially achieved by the removal of gluten, dairy or soy, as well as the addition of vegetables, which are all associated with a decrease in endometriosis-related pain symptoms [7].

In contrast to the current results, Krabbenborg et al. (2021) reported no significant impact of various dietary interventions (i.e. the endometriosis diet, Low FODMAP diet, a gluten-free diet and a low-carbohydrate diet) on QoL in women diagnosed with endometriosis. However, 71.3% of their studied dietary adjustments were reported by women to contribute to the reduction of their chronic endometriosis symptoms [13]. An explanation might be that experiencing more control over endometriosis symptoms through self-management can be a contributing factor to the effectiveness of the endometriosis diet.

The need for self-management is fueled by the severity of endometriosis, the lack of curative treatment and its impact on women's QoL. This has also been observed in a recent Australian survey by Armour et al. (2019), where 76% of endometriosis patients used self-management strategies. Of their participants, 44% used dietary adjustments in order to complement their endometriosis treatment [9]. Moreover, a recent cross-sectional online survey showed that endometriosis patients may experience a higher physical and mental QoL and are able to manage their chronic pain better when they apply these self-management strategies [11]. The current study found that women diagnosed with endometriosis up to 10 years ago, compared to women diagnosed more than 10 years ago, significantly more often adhered to the endometriosis diet. This may be attributed to the fact that a dietary intervention as an addition to standard endometriosis treatment is a relatively new development. Women diagnosed with endometriosis more recently may have a greater need for information about the disease and its possible treatments and are therefore more likely to encounter dietary interventions such as the endometriosis diet when visiting online platforms. Women diagnosed longer ago may consider themselves more knowledgeable about endometriosis and may not search for information or be in less need of it. This can result in them not encountering information on dietary interventions. This study investigated a subset of women about reasons for discontinuing the diet. The majority of women stopped the diet due to the lack of a beneficial effect. The diet being too complex and time-consuming were other reasons for women to discontinue the endometriosis diet. This may indicate that consulting a dietician could be of added value for women with endometriosis considering use of the endometriosis diet. Moreover, dieticians can make sure that a balanced diet is used, avoiding nutritional deficiencies that may arise when patients eliminate important nutrients on their own initiative, without attention to the correct dietary replacement [7].

The additional costs of the endometriosis diet have not yet been studied. However, Saulle et al. (2013) studied the additional costs when adhering to the Mediterranean diet. Be-

cause the two diets are similar, the costs are expected to be comparable. Adherence to the Mediterranean diet cost an additional €0.71 per 1000 kcals, compared to a standard diet [19]. In addition, costs for guidance by a dietician varies in the Netherlands, between €63 and €73 per hour. However, the Dutch tax authorities allow women adhering to a dietary intervention to deduct part of these costs, up to €1350 annually, from their tax return. Total costs of adherence to the endometriosis diet are thereby reduced considerably.

The strengths of the current study include the large sample size and the recruitment strategy. The sample size of 211 participants is sufficient to provide reliable results. By recruiting participants through the online platform of the patients' association (the Dutch Endometriosis Society), a population representative of the Dutch population of women with endometriosis was obtained. The study also has several limitations. First, as it has a cross-sectional design it may not provide definite information about cause-and-effect relationships. Therefore, the observed effect on the QoL cannot be attributed with complete certainty to the endometriosis diet itself. Furthermore, no possible confounders for QoL were studied, such as body mass index, possible stress experienced by the participants in their daily life, their current treatment method and social support. Second, the diagnosis of endometriosis was self-reported. To improve reliability, a diagnosis confirmed by radiological imaging and/or surgery would have been preferable. However, a large study that compared four international cohorts found that women were able to self-report their endometriosis diagnosis accurately, with an overall confirmation proportion of 84% [20]. Moreover, because the questionnaire was distributed through the Dutch patient organization for endometriosis, it is considered that the probability that women were actually diagnosed with endometriosis to be high. Although some of the participants did not know the severity of their disease, it is debatable whether this information is important. Incoherency is often seen between severity of disease and severity of endometriosis symptoms and the impact on QoL. As found in a recent study, only dyspareunia seems to be associated with severity of disease. There was no significant association between severity in other endometriosis-related symptoms and severity of disease [21].

The endometriosis diet is developed by endometriosis patients, based on their experiences and thoughts. Therefore, it lacks standardization and needs to be validated in future research. This study also applied a cut-off value of ≥8 for strict adherence to the diet; this was based on the median and not on the outcome of previous studies, as they were not available. No detailed follow-up questions were asked on their strictness, such as adherence during social events or holidays, or number of days they adhered to the diet during the week or month. This limits the details obtained on diet adherence and strictness of the participants. Finally, the conversation tool 'My Positive Health' is not a validated questionnaire to assess QoL in endometriosis patients, whereas the EHP-30 questionnaire is validated for this assessment [16-18,22]. Nevertheless, the 'My Positive Health'

questionnaire is a frequently used tool in the setting of general practitioners to measure QoL [16,17]. Despite the limitations, these results provide an intriguing picture of women's experiences with the use of the endometriosis diet and emphasizes the importance of more research in order to clarify the mechanism of this beneficial effect and to identify facilitators and barriers of dietary adjustments in patients with endometriosis.

CONCLUSION

In conclusion, this study found that women diagnosed with endometriosis and adhering to the endometriosis diet reported a significantly better QoL compared to women who did not adhere to the diet. Women reported an even higher QoL when strictly adhering to the diet. It is important to increase knowledge regarding the contribution of a dietary intervention on the improvement of endometriosis-related symptoms, and thus the QoL. Therefore, future research should focus on broadening the knowledge on frequently applied dietary interventions such as the endometriosis diet and low FODMAP diet. Finally, it is important to develop a guideline with regard to dietary interventions, so that they can be applied as homogeneously as possible in the future.

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Chapter 9

The effect of dietary interventions on pain and quality of life in women diagnosed with endometriosis: a prospective study with control group

Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Stijn Vlek, Jurriaan Tuynman, Bianca De Bie, Aileen de Vogel, Madelon van Wely, Velja Mijatovic

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ABSTRACT

Study question: What is the influence of dietary interventions, namely the low fermentable oligo-, di-, mono-saccharides, and polyols (Low FODMAP) diet and endometriosis diet, on endometriosis-related pain and quality of life (QoL) compared to a control group?

Summary answer: After adhering to a dietary intervention for 6 months, women with endometriosis reported less pain and an improved QoL compared to baseline whereas, compared to the control group, they reported less bloating and a better QoL in 3 of 11 domains.

What is known already: Standard endometriosis treatment can be insufficient or may be accompanied by unacceptable side effects. This has resulted in an increasing interest in self-management strategies, including the appliance of the Low FODMAP diet and the endometriosis diet (an experience-based avoidance diet, developed by women with endometriosis). The Low FODMAP diet has previously been found effective in reducing endometriosis-related pain symptoms, whereas only limited studies are available on the efficacy of the endometriosis diet. A survey study recently found the endometriosis diet effective in improving QoL but currently no guidelines on use of the diet exist.

Study design, size, duration: A prospective one-center pilot study was performed between April 2021 and December 2022. Participants could choose between adherence to a diet-the Low FODMAP diet or endometriosis diet-or no diet (control group). Women adhering to a diet received extensive guidance from a dietician in training. The follow-up period was 6 months for all three groups. For all outcomes, women adhering to the diets were compared to their baseline situation and to the control group.

Participants/materials, setting, methods: We included women diagnosed with endometriosis (surgically and/or by radiologic imaging) who reported pain scores ≥3 cm on the visual analogue score (0-10 cm) for dysmenorrhea, deep dyspareunia, and/or chronic pelvic pain. The primary endpoint focused on pain reduction for all pain symptoms, including dysuria, bloating, and tiredness. Secondary endpoints, assessed via questionnaires, focused on QoL, gastro-intestinal health, and diet adherence.

Main results and the role of chance: A total of 62 participants were included in the low FODMAP diet (n = 22), endometriosis diet (n = 21), and control group (n = 19). Compared to their baseline pain scores, participants adhering to a diet reported less pain in four of six symptoms (range $P < 0.001$ to $P = 0.012$) and better scores in 6 of 11 QoL domains (range $P < 0.001$ to $P = 0.023$) after 6 months. Compared to the control group, analyzed longitudinally over the 6-month follow-up period, participants applying a diet reported

significant less bloating (P = 0.049), and better scores in 2 of 11 QoL domains (P = 0.004 and P = 0.005).

Limitations, reasons for caution: No sample size was calculated since efficacy data were lacking in the literature. In order to optimize dietary adherence, randomization was not applied, possibly resulting in selection bias.

Wider implications of the findings: Our study suggests that women could benefit from adherence to a dietary intervention, since we found lower pain scores and better QoL after 6 months. However, caution is implied since this is a pilot study, no sample size was calculated, and data on long-term effects (>6 months) are lacking. The results of this pilot study underline the importance of further research and the drawing up of guidelines.

INTRODUCTION

Endometriosis is characterized by the presence of endometrium-like tissue outside the uterus, and can be described as an estrogen-dependent, chronic inflammatory systemic condition [1]. Endometriosis affects ~10% of women of reproductive age worldwide. Symptoms associated with endometriosis can be cyclical, including dysmenorrhea, dyschezia and dysuria, and non-cyclical, including chronic pelvic pain, deep dyspareunia and infertility [1,2]. Other symptoms occurring with endometriosis, such as bloating, abdominal cramping, back pain and fatigue, may overlap with chronic pain conditions such as irritable bowel syndrome (IBS). This overlap in addition to the lack of endometriosis-specific symptoms and available biomarkers may contribute to the current diagnostic delay of 3 –11 years [3-5]. Treatment options for endometriosis include hormonal therapy, surgery, pain management, and/or treatment with ART [1]. However, these medical options can be insufficient in treating symptoms or may be accompanied with unacceptable side effects. Surgery may be accompanied by complications and its effect may diminish in time, leading to recurrence of endometriosis lesions after surgery, especially in hormonally untreated patients. The recurrence of endometriosis lesions often results in the recurrence of symptoms [6-8]. Previous research found that endometriosis and the associated symptoms can negatively affect both mental and physical quality of life (QoL) [9-11]. Therefore, there has been an increasing interest among women with endometriosis in the application of self-management strategies such as meditation, breathing exercises, acupuncture, the use of cannabis — or Cannabidiol (CBD) oil — and dietary interventions [12]. The appliance of self-management strategies was recently found to be associated with a positive effect on physical and mental QoL [13]. In recent years, several studies have been performed on the effect of an adjustment in nutrient intake on endometriosis-related symptoms and QoL. According to a recent systematic review, the addition of certain nutrients (e.g. omega-3 and -6, several vitamins and minerals) and the avoidance of other nutrients (e.g. gluten and soy) had a positive effect on endometriosis-related symptoms [14]. This finding was confirmed by a study that found that supplements, such as omega-3, had a positive effect on endometriosis-associated pain [15]. Studies on the effectiveness of dietary interventions commonly used by women with endometriosis (i.e. a gluten free or lactose free diet) are limited. Nevertheless, in these limited studies the dietary interventions have been found effective in managing endometriosis-related symptoms. However, the mechanisms of action involved are largely unknown [4,16-18].

The low fermentable oligo-, di-, mono-saccharides, and polyols (Low FODMAP) diet, developed by Australian researchers a decade ago, has been studied frequently. It is considered the most effective diet for treating IBS-related symptoms [19]. Monash University has developed a guideline on the implementation of the Low FODMAP diet [20,21]. Additionally, the study by Moore et al. (2017) suggested a specific effect of the Low FODMAP diet on endometriosis-related symptoms. They found that the Low FODMAP diet was

significantly more effective in reducing pain symptoms in women diagnosed with both IBS and endometriosis compared to women diagnosed with IBS alone [4,17]. In contrast to the Low FODMAP diet, the endometriosis diet is an experience-based diet developed and frequently applied by women with endometriosis in the Netherlands. Evidence regarding the efficacy of the endometriosis diet is very limited and currently no guidelines on the use, or the exact composition, of the endometriosis diet exist [22-24]. In addition, there are indications that the consumption of some nutrients, such as gluten or dairy, which are avoided when applying the endometriosis diet, could be beneficial for the composition of the gut microbiome and are part of a fully-fledged diet. Finally, data regarding possible negative effects of these diets owing to the removal of essential nutrients and its effect on health are lacking. Therefore, independently applying the endometriosis diet currently is not recommended by dieticians. Dietary guidance is needed to ensure a fully-fledged diet and one that is based on the patients' symptom pattern [14,25,26].

However, a recently published survey found that adherence to the endometriosis diet was associated with a significantly higher QoL among women with endometriosis, when compared to non-diet adherence. Strict adherence to the diet showed higher scores in all QoL domains when compared to less strict adherence [24]. Non-medical interventions, such as dietary adjustments and interventions, are discussed in the 2022 ESHRE guideline on the management of endometriosis [1]. It is recommended to discuss the application of a dietary intervention with the patient. However, since data on long-term effects and possible harmful effects are lacking, no specific recommendations are made on the appliance of a dietary intervention in women with endometriosis [1]. It is therefore currently not possible to provide a sufficient scientifically substantiated answer to the question frequently asked in daily practice by women diagnosed with endometriosis, of whether they should apply a dietary intervention for their symptoms. Therefore, the objective of this study was to broaden our knowledge and determine the impact of two dietary interventions, namely the Low FODMAP diet and the endometriosis diet, on endometriosis-related (pain) symptoms and QoL. The two diets are commonly used by women with endometriosis. The aim was to evaluate their capacity to reduce pain symptoms and improve QoL, as well as to identify facilitators and barriers of dietary adjustments. The two dietary interventions were compared to a control group of women not adhering to a diet. To the best of our knowledge, this approach not yet been applied in previous studies.

METHODS AND MATERIALS

This prospective pilot study was performed at the Endometriosis Center of the Amsterdam University Medical Center, Amsterdam, the Netherlands. It was conducted between April 2021 and December 2022. The study was approved by the institutional review board of the Amsterdam UMC and was retrospectively registered at www.clinicaltrials.gov (ref-

erence number NCT05714189), because of the temporary hiatus between the closure of the Dutch Trial Register and the possibility to register them at www.clinicaltrials.gov.

Women screened for participation were all diagnosed with endometriosis, either through radiologic imaging (transvaginal ultrasound and/or MRI) or laparoscopy. Women were eligible for participation when they experienced insufficient benefit from their current medical treatment, with a reported pain score of ≥3 (visual analogue score (VAS), scale 0–10 cm) in one or more of the following symptoms: dysmenorrhea, deep dyspareunia, and chronic pelvic pain. Women were excluded when they had undergone surgery in the 6 weeks prior to study enrollment, when they were to undergo surgery within the next 6 months, or when a switch in hormonal therapy within 6 weeks was imminent. In addition, women were excluded if they were pregnant, breastfeeding, diagnosed with a malignancy, or if they were additionally diagnosed with irritable bowel disease and/or lactose intolerance. Finally, women had to be sufficiently fluent in the Dutch or English language.

As this was a pilot study, we aimed to include 20 participants per group, resulting in a total of 60 study participants. During the inclusion period, seven women were lost to follow up after they signed their informed consent but prior to them starting a diet or adherence to the control group. Furthermore, one participant decided to withdraw from the study after adhering to her chosen dietary intervention for 3 weeks. Two participants withdrew from study participation after adhering to their chosen dietary intervention for 6 weeks. We therefore continued inclusion after we reached 60 participants, aiming to include 20 participants per group. Replacements were sought and found for the participants that withdrew from study participation, resulting in a total study population of 62 patients available for analysis.

The dietary interventions

To optimize diet adherence, participants were able to choose between the dietary interventions (the Low FODMAP diet or the endometriosis diet or the control group) rather than being randomized. When adhering to one of the two dietary interventions, participants were extensively guided by a dietician in training over a period of 3 months. Guidance from a dietician when applying a dietary intervention is encouraged because the independent avoidance by patients of (unnecessary) nutrients and/or certain foods can lead to an incomplete diet. The dietician in training was supervised by a dietician registered in the Paramedics Quality Register.

Subsequently participants were asked to continue adherence to the diet without guidance for another 3 months. The dietary guidance was based on the Dutch dietary guideline for Diverticular Disease and IBS and the Dutch dietary guideline for Inflammatory Bowel Diseases [27,28]. Every participant received the same dietary guidance during

the course of the study. A fixed structure of guidance for both dietary interventions was initiated in accordance with the six steps of methodical action [29]. The dietary guidance for both dietary interventions consisted of three 1-h consultations and three short 30-min consultations. Before each initial consultation, participants were asked to complete a food diary for 3 days to monitor their eating behavior. For the Low FODMAP diet, participants had two consultations for each phase: the elimination phase, reintroduction phase, and personalization phase. Since no dietary guideline currently exists for the endometriosis diet, the dietary treatment design of the Low FODMAP diet was also applied for the endometriosis diet. The dietary guidance was concluded with a final interview at the end of the study, where advice for the long term was given if participants decided they wanted to continue their chosen dietary intervention. When participants decided they did not want to adhere to a dietary intervention, they could be part of the control group. The control group received care as usual without a dietary intervention or guidance by a dietician in training. There was no cross-over between the two dietary interventions and the no-diet group.

To support participants in this study that chose to adhere to a diet, tools were distributed to optimize their diet adherence. For participants adhering to the endometriosis diet, specially developed materials, mostly consisting of suitable recipes, were supplied. For participants adhering to the Low FODMAP diet, specially developed materials, consisting of weekly menus, checklists regarding nutrients or the amount that women could or could not eat and grocery lists, were supplied. Finally, the dietician in training developed a food guide containing practical tips and information making adherence to both dietary interventions easier. All participants were asked to complete three sets of questionnaires over a period of 6 months. They were distributed at the start of the study (T0), at 3 months follow-up (T1), and at 6 months follow-up, at the end of the study (T2). All three sets of questionnaires contained questions on the participants' pain scores, expressed using the VAS (scale 0–10 cm) for the symptoms dysmenorrhea, deep dyspareunia, chronic pelvic pain, dysuria, tiredness, and bloating. In addition, the Gastro-Intestinal Quality of Life Index (GIQLI) questionnaire, used to calculate gastro-intestinal health, was included in all three sets of questionnaires. The GIQLI score ranges from 0 to 144, where 0 represents the worst possible gastro-intestinal health and 144 represents the best possible gastro-intestinal health. Finally, all sets of questionnaires contained a questionnaire to specify QoL: the Endometriosis Health Profile (EHP-30) questionnaire. The EHP-30 is validated for use in the Dutch language [30,31]. Using the EHP-30, different scores can be calculated for five core QoL domains (pain, powerlessness, emotional wellbeing, social support, self-image) and six modular QoL domains (work life, children, sexual intercourse, medical profession, treatment, and infertility). The QoL scores range from 0 to 100, where 0 represents best possible health status and 100 the worst possible health status.

For all groups, the first set of questionnaires, distributed at the start of the study (T0), contained a questionnaire measuring basic demographics (e.g. length, weight), the participants' level of education, the Bristol Stool chart [32] and whether the participant had ever adhered to a diet before. When adhering to a dietary intervention, the second and third set of questionnaires, distributed at 3 months (T1) and at 6 months follow-up (T2), respectively, contained a questionnaire with self-composed questions on the participants' self-reported strictness score (in VAS) and adherence to their chosen diet. Finally, the third set of questionnaires distributed at 6 months follow-up (T2) contained a questionnaire for the dietary intervention group only measuring the participants satisfaction with the guidance provided by the dietician in training.

The Low FODMAP diet

FODMAPs are a large class of small non-digestible carbohydrates, which can be found in all kinds of nutrients such as fruits, vegetables, honey, sweeteners, and milk and dairy products. Because of their osmotic activity, FODMAPs force water into the gastro-intestinal tract, resulting in the presentation of a food that is easy for the intestinal microbiota in the large intestine to use. This in turn results in fermentation and increased gas production in the large intestine causing luminal distention. All this can result in symptoms such as bloating, flatulence, abdominal pain, and constipation [17,20,21]. The Low FODMAP diet was initially developed for patients diagnosed with IBS. It is currently recommended by the American College of Gastroenterology for the improvement of IBS symptoms, especially in patients that see a link between food, eating, and their IBS symptoms [20,21]. When applying the Low FODMAP diet, IBS symptoms, such as bloating and abdominal pain, are the most likely to improve but one may additionally see improvements in fatigue, bowel movements, and QoL as well [17,21,33].

The Low FODMAP diet is an avoidance diet and consists of three phases. In the first phase, all nutrients high in FODMAPs (high-FODMAPS) are eliminated from the daily diet over a period of 6–10 weeks to calm down the bowel. After all IBS symptoms are reduced or have even disappeared, patients can continue to the second phase where FODMAP challenges are added. The patient continues the Low FODMAP diet but reintroduces one high-FODMAP nutrient once every 3 days to see whether this exposure causes IBS symptoms. When it does not cause any symptoms, the patient can continue eating this high-FODMAP group in their future daily diet. After each FODMAP challenge, patients will avoid all high-FODMAPS again. Patients can continue to the third and final phase when all FODMAP-challenges are tested. During this phase, the diet is fully personalized and is based on whether the patient tolerated the high-FODMAP nutrient or not during the FODMAP challenges. Only when the high-FODMAP nutrient was not tolerated is it advised to permanently remove it from the daily diet. The Monash University has developed several apps and cookbooks to support women who adhere to the Low FODMAP diet. Our study participants were advised to use them during the course of the study [21].

The endometriosis diet

The endometriosis diet is an avoidance diet developed by women with endometriosis (www.endometriose.nl, Endometriosestichting, 2023). With the endometriosis diet, women avoid nutrients they noticed provoked or aggravated their endometriosis-related symptoms. For this study, we standardized the diet. We based the contents of the endometriosis diet on a recent survey among Dutch patients with endometriosis where the exact content of the diet was described and its influence on QoL was studied [24]. The endometriosis diet and its composition is described in Table 1. During dietary guidance it was ensured that the participants had a fully-fledged diet, despite the fact that certain nutrients were avoided as part of the endometriosis diet.

Outcomes

The primary outcome focused on pain scores (the VAS, scale 0–10 cm) of the endometriosis-related symptoms dysmenorrhea, deep dyspareunia, chronic pelvic pain, dysuria, tiredness, and bloating. The secondary outcomes focused on QoL (EHP-30 questionnaire), gastro-intestinal health (GIQLI questionnaire), and adhesion to the dietary intervention. For all outcomes, women adhering to the diets were compared to their baseline situation and to the control group.

Data collection and analysis

Data were collected using Castor EDC (Castor Electronic Data Capture, Ciwit BV, Amsterdam, the Netherlands) and analyzed using IBM SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Because replacement was sought for the participants that withdrew from participation 3–6 weeks after starting their dietary intervention, data were analyzed according to the per-protocol principle. To optimize result liability, data were additionally analyzed according to the intention-to-treat principle. Baseline characteristics were presented as continuous variables using descriptive statistics with mean and SD for normally distributed data and median with interquartile ranges (IQR) for non-normally distributed data. Categorical variables were presented as absolute numbers and percentages. Differences between baseline characteristics and pain scores between baseline and 6-month follow-up were calculated using the independent Student's t-test when there was normally distributed data, and the Mann–Whitney U test when there was non-normally distributed data. Differences between the control group and intervention group, analyzed longitudinally over the course of the 6-month follow-up period, were calculated using linear mixed models analysis. The influence of self-reported strictness on pain scores was calculated using a logistic regression. Two-sided P-values of <0.05 were considered to indicate statistical significance. Since this was a pilot study, no sample size calculation was performed.

Table 1. Avoidance of nutrients considered part of the endometriosis diet.

Nutrient group	Examples
Red meat	Beef, pork, lamb, mutton, veal, horse, liver
Gluten	(Khorasan) wheat, rye, spelt, barley
Lactose	A sugar found in e.g. milk, cheese spreads, whey-based soft drinks, ice cream
Sugars	All added sugars. Refined sugars (cane sugar, caster sugar), natural sugars (honey, palm sugar) and sweeteners (aspartame, cyclamate, saccharin, sucralose, polyols)
Nutrients high in estrogen	Soy (soymilk, tofu, soya sprout, miso, tempeh, soy sauce, natto), linseed, sesame seeds, black beans
Limited caffeine (max 200 mg daily)	Coffee, tea (black tea, green tea, white tea), soft drinks (coca cola, iced tea, energy drinks/shots, chocolate milk), other (dark and/or milk chocolate, pain killer with added caffeine)

RESULTS

Between April 2021 and August 2022, 140 women indicated they were interested in study participation. Ultimately, 62 women were included in the analysis (Figure 1).
A total of 43 participants chose to adhere to a diet, of which 22 participants chose to adhere to the Low FODMAP diet and 21 participants chose to adhere to the endometriosis diet. A total of 19 participants decided not to adhere to any diet, and therefore be part of the control group.

All patients' characteristics are presented in Table 2. No statistically significant differences were seen in baseline characteristics between diet users and controls (Table 2). All participants adhering to a diet reported significantly less deep dyspareunia, dysuria, bloating, and tiredness after adhering to the diet for 6 months compared to their baseline scores (range $P < 0.001$ to $P = 0.012$). Participants adhering to the Low FODMAP diet reported significantly less dysuria ($P = 0.015$) and bloating ($P < 0.001$), whereas participants adhering to the endometriosis diet reported significant less bloating ($P < 0.001$) and tiredness ($P = 0.002$) after 6 months compared to their baseline scores. Participants in the control group reported no significantly different pain scores in endometriosis-related symptoms at 6 months follow-up (Supplementary Table S1). In addition, the influence of self-reported strictness score on pain was studied. No significant influence of dietary strictness on the reported pain scores was found (Supplementary Table S2).

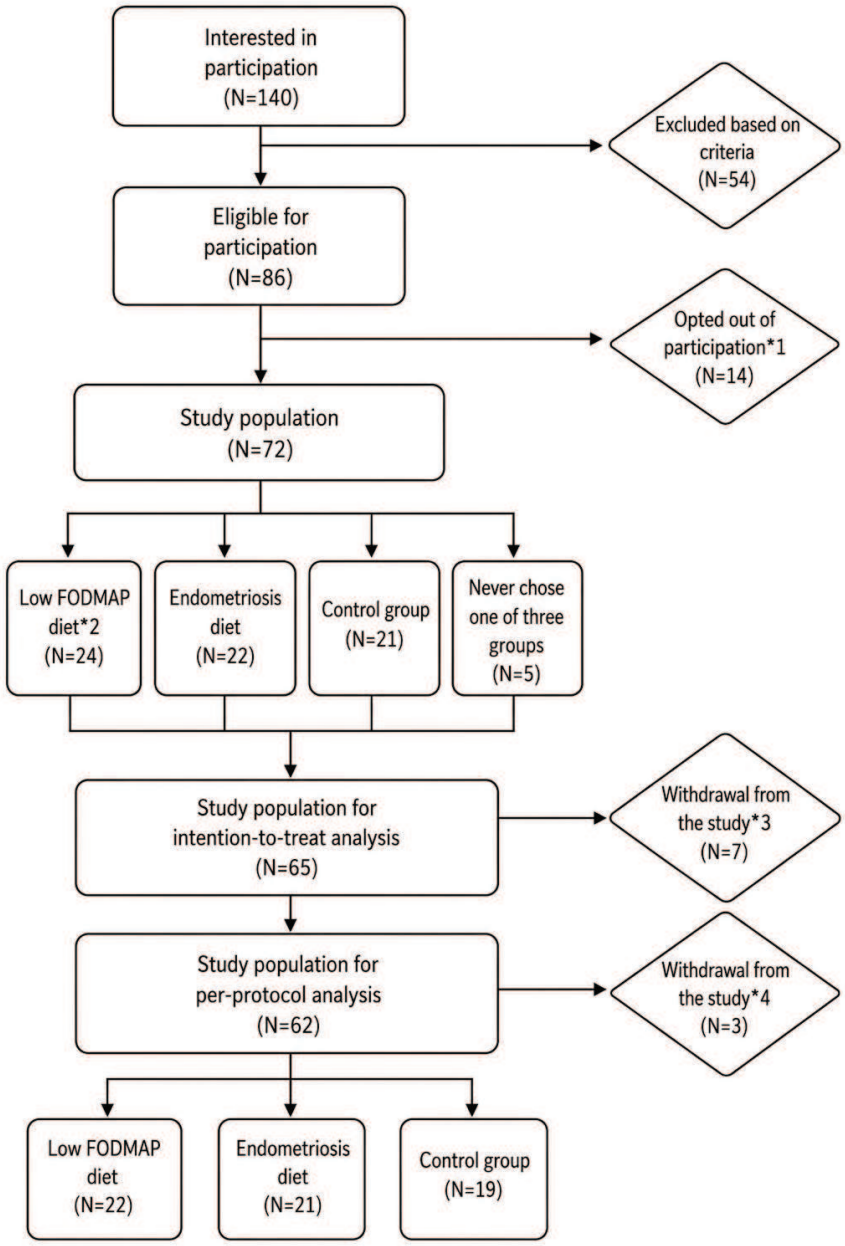

Figure 1. Flowchart of patient recruitment and inclusion in a prospective study of the effect of diet on pain and quality of life in women with endometriosis.

[1] Opted out of participation because they already started the diet somewhere else, found the diet too drastic or we never heard from them again. [2] FODMAP: fermentable oligo-, di-, mono-saccharides, and polyols. [3] Number of women that withdrew from the study after signing their permission form, but prior to starting their diet or adherence to the control group. [4] Withdrawal from the study after adhering to the diet either for 3 or 6 weeks.

When compared to the control group, analyzed longitudinally over the course of the 6 months follow-up period, participants adhering to a dietary intervention experienced significantly less bloating, with a mean difference (MD) of −0.84 (P = 0.049). When analyzing data according to the intention-to-treat principle, this difference lost statistical significance. In addition, compared to the control group, participants adhering to the Low FODMAP diet reported less deep dyspareunia (MD −1.15; P = 0.032) whereas participants adhering to the endometriosis diet reported less bloating (MD −0.99, P = 0.041). When analyzing the data according to the intention-to-treat principle, this MD in deep dyspareunia for women adhering to the Low FODMAP diet and bloating for women adhering to the endometriosis diet was smaller but nevertheless remained significant (Table 3).

QoL was assessed using the EHP-30 questionnaire, and scores were calculated for all QoL domains. All participants adhering to a diet scored significantly better in the domains pain, powerlessness, emotional wellbeing, self-image, work life, and sexual intercourse after adhering to the diet for 6 months compared to their baseline QoL scores (range P < 0.001 to P = 0.023). Participants adhering to the Low FODMAP diet reported significantly better scores after 6 months compared to their baseline scores in the QoL domains pain, powerlessness, and work life (P = 0.007, P = 0.002, and P = 0.013, respectively) whereas participants adhering to the endometriosis diet reported significantly better scores in the QoL domains powerlessness, emotional wellbeing, self-image, and treatment (range P < 0.001 to P = 0.023). Participants in the control group reported no significant differences in QoL after 6 months (Supplementary Table S3).

When comparing them to the control group, analyzed longitudinally over the course of the 6 months follow-up period, participants adhering to a dietary intervention reported significantly better scores in the QoL domains social support (MD −11.26; P = 0.004) and medical profession (MD −17.96; P = 0.005). When analyzing data according to the intention-to-treat principle, only a significant difference in social support remained. Compared to the control group, participants adhering to the Low FODMAP diet reported a better score in the QoL domain medical profession (MD −17.14, P = 0.018) whereas participants adhering to the endometriosis diet reported significant scores in the QoL domains social support (MD −15.47; P < 0.001) and medical profession (MD −18.71; P = 0.010). When analyzing the data according to the intention-to-treat principle, these MDs in medical profession for women adhering to the Low FODMAP diet and in social support and medical profession for women adhering to the endometriosis diet were smaller but nevertheless remained significant (Table 4).

Participants adhering to a diet experienced better gastro-intestinal health, measured using the GIQLI questionnaire, after adhering to the diet for 6 months compared to their baseline scores (P < 0.001) (Supplementary Table S4). However, when comparing data to the control group, analyzed longitudinally over the course of the 6 months follow-up

period, participants adhering to a dietary intervention reported no improvement in gastro-intestinal health (Table 5).

Results for patient experiences

Participants had different motivations to participate in the dietary intervention. Mostly, they hoped it would decrease their pain symptoms, would reduce their bowel symptoms, such as flatulence and bloating, and would optimize their general health. At the start of their diet, most participants found adherence to the diet difficult whereas by the 6 months follow-up they found adherence to the diet less difficult (difficulty 'normal'), indicating normalization toward dealing with a diet in daily life (Low FODMAP diet $P < 0.001$ and endometriosis diet $P = 0.017$). Difficulties most frequently reported were high costs, the time-consuming element and other difficulties such as adherence to the diet in a social setting, i.e. when going out for dinner or eating with friends and family. Almost all participants completed 6 months adherence to their diet (40/43). Three participants decided to discontinue their diet prematurely because of personal circumstances such as moving to another country (n = 1) or an illness in the family (n = 1). One participant did not give any details regarding her personal circumstances leading the discontinuation of her diet. There was no cross-over by participants to the other dietary intervention. No participants experienced side effects from their chosen dietary intervention. Finally, the majority of participants expressed that they would (partially) continue their diet at the end of the study (80.6% in endometriosis diet versus 81.8% Low FODMAP diet) (Supplementary Table S5).

Table 2. Patient characteristics of all three groups, including women adhering to the Low FODMAP diet, endometriosis diet, or no diet (control group).

Patient characteristics	Low FODMAP diet (n=22)	Endometriosis diet (n=21)	Control group (n=19)	P-value
Age in years (mean (SD))	36.9 (5.9)	39.1 (15.8)[1]	37.6 (8.5)	0.593
BMI (mean (SD))	26.0 (4.4)	24.3 (3.3)	25.4 (4.4)	0.490
Lifestyle (%)				
Smoking	1 (4.5%)	0 (0%)	3 (15.8%)	
Alcohol usage	16 (72.7%)	8 (38.1%)	9 (47.4%)	
Family composition (%)				
Single	6 (27.3%)	1 (4.8%)	2 (10.5%)	
Living with housemate, partner and/or children	14 (63.6%)	20 (95.2%)	15 (78.9%)	
Unknown	2 (9.1%)	0 (0%)	2 (10.5%)	
Educational attainment (%)				
High School	1 (4.5%)	0 (0%)	0 (0%)	
Intermediate or Higher Vocational Education	9 (40.9%)	15 (71.4%)	15 (78.9%)	

Table 2. Patient characteristics of all three groups, including women adhering to the Low FODMAP diet, endometriosis diet, or no diet (control group). (*continued*)

Patient characteristics	Low FODMAP diet (n=22)	Endometriosis diet (n=21)	Control group (n=19)	P-value
University	10 (45.5%)	7 (33.3%)	3 (15.8%)	
Other	1 (4.5%)	0 (0%)	0 (0%)	
Unknown	1 (4.5%)	0 (0%)	1 (5.3%)	
Other conditions				
Gynaecological diagnoses[2]	-	3 (14.3%)	2 (10.5%)	
Gastro-intestinal, liver and urinary diagnoses[3]	2 (9.1%)	2 (9.5%)	4 (21.1%)	
Metabolic disorders[4]	-	-	1 (5.3%)	
Neurological diagnoses[5]	1 (4.5%)	2 (9.5%)	1 (5.3%)	
Endocrine disorders[6]	1 (4.5%)	1 (4.8%)	-	
Hemophilia or cardiovascular disease[7]	1 (4.5%)	2 (9.5%)	-	
Muscle diagnoses (fibromyalgia)	2 (9.1%)	1 (4.8%)	1 (5.3%)	
Atopic diagnoses[8]	2 (9.1%)	3 (14.3%)	1 (5.3%)	
Viral diagnoses (CMV, covid)	2 (9.1%)	-	1 (5.3%)	
Food allergies/sensitivities, vitamin shortage	-	3 (14.3%)	1 (5.3%)	
Previous malignancy	-	-	1 (5.3%)	
Psychological diagnoses[9]	3 (13.6%)	3 (14.3%)	5 (26.3%)	
Years since diagnosis (mean, range)	9.3 (2 – 20 years)	10.3 (2 – 35 years)	9.7 (2 – 26 years)	0.417
Grade of Endometriosis (%)				0.499
Grade I	0 (0%)	0 (0%)	0 (0%)	
Grade II	2 (9.1%)	4 (19.0%)	3 (15.8%)	
Grade III	3 (13.6%)	3 (14.3%)	6 (31.6%)	
Grade IV	13 (59.1%)	13 (61.9%)	8 (42.1%)	
Unknown	4 (18.2%)	1 (4.8%)	2 (10.5%)	
Treatment				0.992
Previous operation	15 (68.2%)	10 (47.6%)	11 (57.9%)	
No previous operation	7 (31.8%)	11 (52.4%)	8 (42.1%)	
Current treatment				0.565
Oral contraceptives	10 (45.5%)	10 (47.6%)	7 (36.9%)	

DISCUSSION

This prospective single-center pilot study aimed to investigate the effect of two dietary interventions on endometriosis-related symptoms and QoL, and compare it to a control group, analyzed longitudinally over the course of a 6-month follow-up period. Our results suggest that women adhering to a dietary intervention experience less non-cyclical deep

Table 2. Patient characteristics of all three groups, including women adhering to the Low FODMAP diet, endometriosis diet, or no diet (control group). (*continued*)

Patient characteristics	Low FODMAP diet (n=22)	Endometriosis diet (n=21)	Control group (n=19)	P-value
GnRH agonist (Lucrin)	2 (9.1%)	2 (9.5%)	2 (10.5%)	
IUD	1 (4.5%)	0 (0%)	0 (0%)	
Oral contraceptives with IUD	2 (9.1%)	1 (4.8%)	2 (10.5%)	
Pain medication	0 (0%)	1 (4.8%)	2 (10.5%)	
Pain medication in addition to hormonal therapy	1 (4.5%)	2 (9.5%)	0 (0%)	
Different treatment	0 (0%)	2 (9.5%)	0 (0%)	
No treatment	6 (27.3%)	3 (14.3%)	6 (31.6%)	

[1] FODMAP: fermentable oligo-, di-, mono-saccharides, and polyols.

[2] Data not normally distributed, therefore shown as median with interquartile range (IQR).

[3] Fibroids, mastopathy, adhesions because of previous operations.

[4] Gastro-esophageal reflux, irritable bowel syndrome (IBS), syndrome of Gilbert, chronic urinary tract infection, and enlarged bladder.

[5] Diabetes.

[6] Migraine, hernia.

[7] Hypothyroidism, Hashimoto.

[8] Hypertension, immune thrombocytopenia (ITP), alpha thalassemia, and previous brain aneurysm.

[9] Asthma/asthmatic bronchitis, eczema, and hay fever.

[10] Depression, bipolar disease, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and chronic fatigue.

[11] ASRM, American Society for Reproductive Medicine.

Table 3. Difference in reported VAS scores for endometriosis-related symptoms between the dietary interventions and control group, compared longitudinally over the follow-up period of 6 months. Mean differences with interquartile ranges (IQR) were calculated using mixed models. Bold values indicate P-values.

	Intervention (Low FODMAP[1] or Endometriosis Diet) n=43				**Control n=19**			
Symptoms associated with endometriosis	**Baseline VAS[2] score (median, IQR)**	**3-month VAS score (median, IQR)**		**6-month VAS score (median, IQR)**	**Baseline VAS score (median, IQR)**	**3-month VAS score (median, IQR)**	**6-month VAS score (median, IQR)**	**Mean Difference[3] (95% CI) P-value**
Dysmenorrhea	5.0 (8.0)	3.28 (3.53)		3.0 (6.0)	4.0 (7.0)	5.0 (7.0)	4.0 (7.0)	-0.36 (-1.45 to 0.73) **0.515**
Deep dyspareunia	4.0 (5.0)	2.41 (2.48)		1.0 (4.0)	3.5 (6.0)	4.0 (5.0)	1.0 (6.0)	-0.83 (-1.74 to 0.08) **0.075**
Chronic Pelvic Pain	2.0 (6.0)	2.34 (2.54)		3.0 (6.0)	2.5 (6.0)	1.0 (5.0)	2.0 (4.0)	-0.014 (-0.94 to 0.91) **0.976**
Dysuria	1.0 (4.0)	0.85 (1.81)		0.0 (1.0)	0.0 (3.0)	1.0 (1.0)	0.0 (1.0)	0.05 (-0.58 to 0.67) **0.880**
Bloating	8.0 (3.5)	3.39 (2.70)		3.0 (4.0)	6.0 (4.0)	6.0 (4.0)	5.0 (5.0)	-0.84 (-1.68 to -0.004) **0.049**
Tiredness	7.0 (4.0)	4.79 (2.58)		5.0 (3.0)	7.0 (2.8)	6.0 (5.0)	6.0 (6.0)	-0.04 (-0.88 to 0.80) **0.924**
	Low FODMAP diet (n=22)				**Endometriosis diet (n=21)**			
Symptoms associated with endometriosis	**Baseline VAS score (median, IQR)**	**3-month VAS score (median, IQR)**	**6-month VAS score (median, IQR)**	**Mean Difference[4] (CI 95%) P-value**	**Baseline VAS score (median, IQR)**	**3-month VAS score (median, IQR)**	**6-month VAS score (median, IQR)**	**Mean Difference[4] (CI 95%) P-value**
Dysmenorrhea	4.0 (7.0)	1.0 (7.0)	2.0 (4.0)	-1.08 (-2.31 to 0.16) **0.087**	6.0 (7.0)	5.0 (8.0)	3.5 (7.0)	0.32 (-0.90 to 1.54) **0.606**

Table 3. Difference in reported VAS scores for endometriosis-related symptoms between the dietary interventions and control group, compared longitudinally over the follow-up period of 6 months. Mean differences with interquartile ranges (IQR) were calculated using mixed models. Bold values indicate P-values. (*continued*)

	Intervention (Low FODMAP[1] or Endometriosis Diet) n=43				**Control n=19**			
Deep dyspareunia	4.5 (6.0)	1.5 (3.0)	0.0 (4.0)	-1.15 (-2.2 to -0.10) **0.032**	4.0 (6.0)	2.0 (6.0)	2.0 (5.0)	-0.55 (-1.58 to 0.49) **0.298**
Chronic Pelvic Pain	2.0 (6.0)	1.0 (4.0)	4.0 (6.0)	-0.11 (-1.17 to 0.96) **0.845**	3.0 (6.0)	2.0 (5.0)	2.5 (5.0)	0.07 (-0.98 to 1.12) **0.894**
Dysuria	1.0 (3.0)	0.0 (0.0)	0.0 (0.0)	-0.19 (-0.90 to 0.53) **0.607**	1.0 (4.5)	0.0 (3.0)	0.0 (1.0)	0.26 (-0.44 to 0.97) **0.464**
Bloating	8.0 (3.8)	3.0 (4.25)	3.0 (4.5)	-0.69 (-1.66 to 0.27) **0.159**	7.0 (3.5)	2.0 (4.0)	2.0 (3.0)	-0.99 (-1.94 to -0.039) **0.041**
Tiredness	7.0 (4.0)	5.0 (5.0)	5.0 (5.0)	0.07 (-0.90 to 1.04) **0.884**	7.0 (5.0)	5.0 (4.0)	3.5 (2.8)	-0.15 (-1.10 to 0.81) **0.761**

[1] FODMAP: fermentable, oligo-, di-, monosaccharides and polyols. [2] VAS: visual analogue scale (scale 0-10cm). [3] Difference calculated between baseline, 12-week and 24-week follow-up, between the two dietary interventions and control group. [4] Difference calculated between baseline, 12-week and 24-week follow-up. Difference calculated between the Low FODMAP diet and control group, and between endometriosis diet and control group.

Table 4. Difference in quality of life domains between the dietary interventions and control group, compared longitudinally over the follow-up period of 6 months. Mean differences with interquartile ranges (IQRs) were calculated using mixed models. Bold values indicate P-values.

	Intervention (Low FODMAP[1] or Endometriosis Diet) n=43			Control n=19			
Domains of Quality of Life (QoL) measured using the EHP-30[2]	**Baseline EHP-30 score (median, IQR)**	**3-month EHP-30 score (median, IQR)**	**6-month EHP-30 score (median, IQR)**	**Baseline EHP-30 score (median, IQR)**	**3-month EHP-30 score (median, IQR)**	**6-month EHP-30 score (median, IQR)**	**Mean Difference[3] (95% CI) P-value**
Pain	42.0 (29.0)	25.0 (39.2)	22.7 (37.5)	28.4 (33.5)	31.8 (13.6)	22.7 (25.0)	-2.41 (-8.97 to 4.15) **0.469**
Powerlessness	50.0 (30.2)	20.8 (29.2)	16.7 (29.2)	35.4 (31.3)	37.5 (12.5)	29.2 (25.0)	-4.31 (-10.86 to 2.24) **0.195**
Emotional Wellbeing	33.3 (33.3)	25.0 (32.3)	20.8 (32.3)	31.3 (26.0)	37.5 (25.0)	16.7 (25.0)	-1.83 (-7.53 to 3.88) **0.528**
Social Support	34.4 (39.1)	37.5 (43.8)	28.1 (31.3)	43.8 (39.1)	50.0 (31.3)	37.5 (18.8)	-11.26 (-18.77 to -3.74) **0.004**
Self-Image	50.0 (43.8)	25.0 (41.7)	25.0 (39.6)	41.7 (27.1)	33.3 (33.3)	25.0 (58.3)	-1.45 (-9.59 to -6.69) **0.726**
Work Life	25.00 (40.0)	7.50 (28.75)	5.0 (25.0)	10.00 (15.0)	15.0 (18.75)	10.0 (22.5)	1.89 (-4.77 to 8.55) **0.576**
Children	0.0 (37.5)	0.0 (21.9)	0.0 (9.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	3.66 (-3.22 to 10.53) **0.295**
Sexual Intercourse	45.0 (51.3)	25.0 (40.0)	27.5 (47.5)	50.0 (42.5)	50.0 (45.0)	15.0 (75.0)	-6.97 (-15.79 to 1.85) **0.120**
Medical Profession	6.3 (37.5)	15.6 (31.3)	12.5 (37.5)	18.8 (37.5)	25.0 (56.3)	40.6 (39.1)	-17.96 (-30.26 to -5.66) **0.005**
Treatment	41.7 (39.6)	37.5 (33.3)	33.3 (41.7)	33.3 (25.0)	25.0 (45.8)	25.0 (66.7)	7.17 (-2.21 to 16.55) **0.132**

Table 4. Difference in quality of life domains between the dietary interventions and control group, compared longitudinally over the follow-up period of 6 months. Mean differences with interquartile ranges (IQRs) were calculated using mixed models. Bold values indicate P-values. (*continued*)

	Intervention (Low FODMAP[1] or Endometriosis Diet) n=43			**Control n=19**				
Infertility	71.9 (32.8)	87.5 (-)	56.3 (56.3)	87.5 (31.3)	75.0 (25.0)	81.3 (-)	-9.37 (-25.60 to 6.86) **0.243**	
	Low FODMAP diet (n=22)				**Endometriosis diet (n=21)**			
Domains of Quality of Life (QoL) measured using the EHP-30	**Baseline EHP-30 score (median, IQR)**	**3-month EHP-30 score (median, IQR)**	**6-month EHP-30 score (median, IQR)**	**Mean Difference (CI 95%)[4] P-value**	**Baseline EHP-30 score (median, IQR)**	**3-month EHP-30 score (median, IQR)**	**6-month EHP-30 score (median, IQR)**	**Mean Difference[4] (CI 95%) P-value**
Pain	43.2 (28.4)	20.5 (34.1)	15.9 (31.8)	-3.60 (-11.15 to 3.95) **0.348**	40.9 (37.5)	29.5 (39.8)	22.7 (50.0)	-1.36 (-8.80 to 6.09) **0.720**
Powerlessness	54.2 (27.1)	20.8 (41.7)	16.7 (37.5)	-1.38 (-8.90 to 6.14) **0.718**	5.8 (43.8)	20.8 (27.1)	16.7 (35.4)	-6.80 (-14.20 to 0.61) **0.072**
Emotional Wellbeing	37.5 (37.5)	25.0 (37.5)	20.8 (37.5)	0.81 (-5.72 to 7.34) **0.807**	33.3 (33.3)	25.0 (20.8)	20.8 (27.1)	-4.15 (-10.58 to 2.28) **0.204**
Social Support	31.3 (40.6)	43.8 (43.8)	31.3 (50.0)	-6.93 (-15.48 to 1.62) **0.111**	37.5 (40.6)	12.5 (46.9)	25.0 (34.4)	-15.47 (-23.89 to -7.06) **<0.001**
Self-Image	50.0 (50.0)	25.0 (41.7)	33.3 (58.3)	1.08 (-8.26 to 10.42) **0.820**	50.0 (37.5)	33.3 (37.5)	16.7 (29.2)	-3.98 (-13.18 to 5.23) **0.395**
Work Life	30.0 (40.0)	5.0 (20.0)	5.0 (25.0)	3.12 (-4.59 to 10.83) **0.425**	22.5 (38.8)	10.0 (32.5)	5.0 (10.0)	0.86 (-6.77 to 8.49) **0.824**

Table 4. Difference in quality of life domains between the dietary interventions and control group, compared longitudinally over the follow-up period of 6 months. Mean differences with interquartile ranges (IQRs) were calculated using mixed models. Bold values indicate P-values. (*continued*)

	Intervention (Low FODMAP[1] or Endometriosis Diet) n=43			**Control n=19**				
Children	0.0 (43.8)	0.0 (12.5)	0.0 (0.0)	4.40 (-3.52 to 12.32) **0.274**	0.0 (37.5)	0.0 (25.0)	0.0 (18.8)	2.99 (-4.80 to 10.78) **0.450**
Sexual Intercourse	45.0 (50.0)	20.0 (40.0)	30.0 (50.0)	-9.97 (-20.09 to 0.14) **0.053**	45.0 (47.5)	30.0 (35.0)	20.0 (50.0)	-4.31 (-14.27 to 5.66) **0.394**
Medical Profession	6.3 (37.5)	15.6 (53.1)	12.5 (18.8)	-17.14 (-31.27 to -3.00) **0.018**	0.0 (43.8)	12.5 (31.3)	6.3 (42.2)	-18.71 (-32.79 to -4.63) **0.010**
Treatment	25.0 (37.5)	33.3 (33.3)	41.7 (37.5)	5.35 (-5.12 to 15.82) **0.312**	50.0 (25.0)	41.7 (41.7)	33.3 (25.0)	9.33 (-1.35 to 20.01) **0.086**
Infertility	68.8 (-)	68.8 (-)	56.3 (-)	-11.88 (-31.66 to 7.90) **0.224**	78.1 (-)	x	56.3 (56.3)	-6.08 (-26.87 to 14.70) **0.550**

[1] FODMAP: fermentable oligo-, di-, mono-saccharides, and polyols. [2] EHP-30 Questionnaire: endometriosis health profile 30 questionnaire (range 0–100). [3] Difference calculated between baseline, 12- and 24-week follow-up, between the two dietary interventions and control group. [4] Difference calculated between baseline, 12- and 24-week follow-up. Difference calculated between the Low FODMAP diet and control group, and between endometriosis diet and control group.

Table 5. Difference in gastro-intestinal quality of life, measured using the gastro-intestinal quality of life index, between the dietary interventions and control group, compared longitudinally over the follow-up period of 6 months. Mean differences with interquartile ranges (IQR) were calculated using mixed models. Bold values indicate P-values.

GIQLI[2] score	**Intervention (Low FODMAP[1] or Endometriosis Diet) n=43**				**Control n=19**			
	Baseline GIQLI-score (mean, SD)	**3-month GIQLI-score (mean, SD)**	**6-month GIQLI-score (mean, SD)**		**Baseline GIQLI-score (mean, SD)**	**3-month GIQLI-score (mean, SD)**	**6-month GIQLI-score (mean, SD)**	**Mean Difference[3] (95% CI) P-value**
	127.35 (14.67)	136.85 (12.79)	139.03 (11.09)		134.29 (14.79)	134.11 (9.34)	133.27 (13.82)	1.31 (-5.49 to 2.88) **0.539**
GIQLI score	**Low FODMAP diet n=22**				**Endometriosis diet n=21**			
	Baseline GIQLI-score (mean, SD)	**3-month GIQLI-score (mean, SD)**	**6-month GIQLI-score (mean, SD)**	**Mean Difference[4] (CI 95%) P-value**	**Baseline GIQLI-score (mean, SD)**	**3-month GIQLI-score (mean, SD)**	**6-month GIQLI-score (mean, SD)**	**Mean Difference[4] (CI 95%) P-value**
	122.68 (14.36)	135.11 (13.89)	136.74 (9.81)	1.58 (-6.32 to 3.16) **0.511**	132.24 (13.66)	138.50 (11.77)	141.10 (11.86)	3.88 (-0.82 to 8.57) **0.105**

[1] FODMAP: fermentable oligo-, di-, mono-saccharides, and polyols. [2] GIQLI: Gastro-Intestinal Quality of Life Index (range 0–144). [3] Difference calculated between baseline, 12- and 24-week follow-up, between the two dietary interventions and control group. [4] Difference calculated between baseline, 12- and 24-week follow-up. Difference calculated between the Low FODMAP diet and control group, and between endometriosis diet and control group.

dyspareunia, cyclical dysuria, bloating, and tiredness after 6 months. Other (non-)cyclical symptoms associated with endometriosis, such as dysmenorrhea and chronic pelvic pain, were not significantly improved. When comparing participants adhering to a dietary intervention to participants in the control group, analyzed longitudinally over the course of the 6-month follow-up period, only a significant difference in bloating remained. Our results additionally suggest that women adhering to a dietary intervention reported better EHP-30 scores in the QoL domains pain, powerlessness, emotional wellbeing, self-image, work life, and sexual intercourse after 6 months. When comparing participants adhering to a dietary intervention to participants in the control group, only a significant difference in social support and medical profession remained. There was a high level of satisfaction with the dietary guidance. Ultimately, 35 out of 43 participants wanted to continue their diet, at least partially, at the end of the 6-month follow-up period.

Clinical implications

To our knowledge, this pilot study is the first to examine the effect of both the Low FODMAP diet and endometriosis diet on endometriosis-related symptoms and QoL in women with endometriosis. In a previous retrospective study using a nationwide survey, our study group found that Dutch women adhering to the endometriosis diet reported significantly improved QoL, especially when there was strict adherence to the diet [24]. Although a positive impact of self-reported diet strictness on pain scores was not observed in our current study, potentially owing to the small sample size, we did observe a positive association between dietary adherence and both pain scores and QoL. Our study suggests that adherence to a dietary intervention could reduce both (non-)cyclical endometriosis-related symptoms and gastro-intestinal symptoms such as bloating. Previously, an overlap was seen between symptoms associated with endometriosis and symptoms associated with IBS [4]. Jess et al. observed that endometriosis was more frequently associated with gastro-intestinal dysfunction, as found in IBS.

In their nationwide Danish cohort of 37 661 women, a significant association between endometriosis and IBS (standardized incidence ratio 1.5 (95% CI 1.3–1.7)) was observed [34]. Additionally, in an Australian cross-sectional survey (N = 484) on self-management strategies among women surgically diagnosed with endometriosis, 44% of respondents adhered to a dietary intervention such as the Low FODMAP diet, gluten free- or lactose-free diet. They found that these dietary interventions were effective in reducing endometriosis-related pelvic pain, as well as gastro-intestinal symptoms such as abdominal discomfort (i.e. flatulence, bloating, and diarrhea) [35]. Comparable results to Armour et al. (2021) were found in a study evaluating the effect of the Low FODMAP diet on endometriosis-related and gastro-intestinal symptoms, in women with endometriosis and IBS [4]. Finally, Sesti et al. (2007) recently studied the effect of treatment on pain symptoms and QoL after conservative pelvic surgery for endometriosis grade III–IV. They found that post-surgical treatment with a dietary intervention was similarly effective as post-surgical

treatment with a GnRH-agonist or continuous oral contraceptives [36]. These studies, in addition to our findings, support the hypothesis that a dietary intervention could improve both endometriosis-related symptoms and gastro-intestinal symptoms.

Therefore, women diagnosed both with endometriosis and a gastro-intestinal diagnosis might benefit most from a dietary intervention. However, since no additional analyses on this were performed in our study, we cannot state this implication with certainty. Contrary to our findings, a cross-sectional survey study on the effect of different, frequently applied diets in Dutch patients with endometriosis did not show any significant differences in QoL between women adhering to a diet and women not adhering to a diet. However, they did find that 224 of the 314 specific dietary adjustments (71.3%) reported by the participants were considered to contribute to the reduction of the participants' chronic endometriosis symptoms [23]. Our pilot study additionally found that adherence to a dietary intervention led to an improvement in QoL. According to Soliman et al. (2017), experiencing more pelvic pain or menstrual cramping, anxiety or stress, fatigue, bloating, and intermenstrual bleeding was associated with a lower QoL [37]. This might explain why our participants, with improved pain scores, additionally reported improved QoL scores. Furthermore, women participating in our study received extensive guidance by the dietician in training for the first 3 months and were provided with tools to optimally adhere to their chosen diet. The active role that participants took in managing their endometriosis-related symptoms may have contributed to a greater sense of control over their endometriosis, possibly contributing to an improved QoL. Previous research has shown that a person-centered approach, in which women were able to take an active role in their disease management and worked together with the healthcare provider aiming to improve their symptoms, resulted in a greater feeling of control over their symptoms and more positive healthcare provider experiences [38]. These studies, in addition to our findings, show that a dietary intervention can improve QoL in women with endometriosis, both through reducing pain symptoms and by empowering women to take an active role in their disease management.

While previous studies have described the positive effects of dietary interventions, such as the Low FODMAP diet, on pain and QoL, they might also have negative effects. There is evidence that the Low FODMAP diet may induce profound changes in the composition and functioning of the gut microbiota. However, there is still a lot of uncertainty regarding this effect. In addition, evidence regarding the long-term effects of the Low FODMAP diet is limited, since most previous studies only had a follow-up period of <12 weeks [19]. Regarding the endometriosis diet, its impact on endometriosis-related symptoms, the long-term effects, and possible negative effects on health have not been investigated in previous studies. Therefore, the endometriosis diet is currently not advised by dieticians in the Netherlands [14]. In the present study, we handled a follow-up period of 6 months (24 weeks) for both diets. However, since this was a pilot study lacking a calculation of

sample size, we cannot attribute with complete certainty all effects on pain and QoL to the dietary interventions. To determine long-term effects with more certainty in future studies, it could be recommended to extend the follow-up period to at least 6 months, similar to our pilot study. This underlines the importance of additional research on the efficacy and safety, including possible negative effects on health, of dietary interventions on endometriosis-related symptoms and associated QoL, with a longer follow-up period.

Adherence to the endometriosis diet or Low FODMAP diet can be associated with higher costs. According to a British study, adherence to the Low FODMAP diet for a period of 6 weeks cost an additional €175.07 (£139.20; exchange rate £1 = €1.2577) [39]. Although the costs of the endometriosis diet have never been studied, the diet is very similar to the Mediterranean diet, which costs an additional €0.71 per 1000 kcal, compared to a standard diet [40]. In our study, dietary guidance was provided free of charge for participants. However, dietary guidance normally costs between €63 and €73 per hour for both dietary interventions in our study. It is thought that an average of two to four guidance sessions, with a total of 5 hours, are needed to optimally adhere to a diet. These costs are not refunded by health insurance in most countries. In the Netherlands only 3 h of dietary guidance are covered by basic health insurance. However, additional costs for adherence to a diet on medical indication, such as higher grocery costs, are tax-deductible in the Netherlands, which can reduce the dietary costs significantly. In 2022, annual dietary costs were tax deductible up to €1350 for the endometriosis diet and up to €1050 for the Low FODMAP diet.

Strengths and limitations

Our study has several strengths. First, very few women discontinued adherence to their chosen diet prematurely and withdrew from study participation. Both the extensive guidance and the information materials contributed to this positive result. The fact that the significant differences were smaller or no longer seen when data were analyzed according to the intention-to-treat principle, where women adhering to their dietary intervention for only 3–6 weeks were included, underlines the importance of adherence to a dietary intervention for a longer period of time. In addition, a guideline for adherence to the endometriosis diet was developed and the composition of the diet was standardized. Finally, our follow-up period spanned a longer time period than previous studies. Our follow-up period entailed 24 weeks, whereas other studies had a follow-up period of 12 weeks at most. This contributes to increasing knowledge on the long-term effects of the dietary adjustments when compared to no diet. Our study also has several limitations. Since this was a pilot study designed to explore the feasibility of treating women with endometriosis with one of two dietary interventions and data were lacking for effect sizes, we were not able to calculate a sample size. Moreover, this was a patient preference study where randomization was not applied. Although this might have induced selection bias, we valued a strong motivation to adhere to a diet, accepting the risk that the partici-

pant pool may not represent the target population. We were not able to generalize our conclusions, as would be the case if the trial was conducted as a randomized controlled trial (RCT). However, we believe that an RCT in dietary interventions will not be feasible as dietary interventions require a very high motivation from participants. Furthermore, the current study design is similar to clinical practice where women decide themselves whether they want to adhere to a dietary intervention or not.

We cannot exclude that the Hawthorne effect somewhat influenced our results. Since women were aware they participated in a trial, adjusted their behavior by altering their diet, and received attention from the dietician in training for 6 months, this could have favorably influenced their reported pain scores and QoL [41]. The effect of the added attention from a dietician would be common practice for all dietary interventions and is impossible to separate from the effect of the diet itself. However, since we advise always having support from a dietician when adjusting a diet, it is not necessary to divide the effects. Finally, some women found it hard to quantify their pain retrospectively using pain scores. They still experienced pain, resulting in them scoring their pain quite high. However, their pain occurred much less frequently, possibly making the quantification of pain using recalled VAS-scores difficult. Van Barneveld et al. (2023) have recently developed an electronic instrument to objectify symptoms in women with endometriosis. In their study, women were asked to register their pain scores at random moments over a period of 1 week, 10 times a day. They found that these random pain scores were significantly lower compared to the reported 'recalled' pain scores requested at the end of the week. Perhaps this pain tool would have been more effective in objectifying the pain scores of our participants [42]. Despite these limitations, our study paints a promising picture of the effect of the Low FODMAP diet and endometriosis diet on endometriosis-related symptoms and QoL.

CONCLUSION

With our study, we have aimed to provide a more scientifically substantiated answer to the question in daily practice of women diagnosed with endometriosis, of whether they should apply a dietary intervention for their symptoms. Our study suggests that women adhering to a diet experience less pain and improved QoL after 6 months. When comparing it to the control group, analyzed longitudinally over the 6 months follow-up period, only significantly less bloating and improved scores in the QoL domains medical treatment and social support were seen in women adhering to a dietary intervention. Therefore, applying a dietary intervention to women diagnosed with endometriosis could be discussed during counseling, especially when (hormonal) therapy and surgery fail to completely eliminate their symptoms and there is a wish for self-management of their chronic pain complaints. However, several possibly problematic issues should be

discussed with the patient such as the additional costs and the uncertainty regarding possible negative effects. Therefore, women should be encouraged to seek help from a dietician when applying a new diet, also to ensure a fully-fledged diet. Since this is a pilot study without a calculated sample size, we cannot attribute the positive effects with complete certainty to a dietary intervention. For future studies calculating a sample size, based on the findings of this study a follow-up period of at least 6 months, and increasing knowledge regarding possible negative effects of the dietary interventions, is recommended.

QR code to article for supplementary materials



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Chapter 10

Diet associations in endometriosis: a critical narrative assessment with special reference to gluten

Fred Brouns, Annelotte van Haaps, Daniël Keszthelyi, Koen Venema, Marlies Bongers, Jacques Maas, Velja Mijatovic

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ABSTRACT

Endometriosis is characterized by the presence of endometrium-like tissue outside the uterus. The etiology remains largely unknown. Despite adequate treatment, patients can still experience symptoms or side effects resulting in therapy incompliance and in self-management strategies such as dietary measures is increasing. A gluten free diet is thought to be contributory in reducing endometriosis-related pain, thereby optimizing quality of life. However, data is conflicting and currently provides no evidence for causality. This narrative review aims to put the effect of dietary self-management strategies on endometriosis in a balanced perspective, especially the effect of gluten and a gluten free diet. Several studies have found a strong overlap in symptoms, metabolic and immune responses associated with endometriosis and those associated with celiac disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome and non-celiac wheat sensitivity. However, it remains unclear whether these diseases and/or disorders are causal to an increased risk of endometriosis.

Some studies have found a positive effect on the risk of endometriosis, endometriosis-related symptoms and quality of life (QoL) when women either avoided certain nutrients or foods, or applied a specific nutrient supplementation. This includes the avoidance of red meat, an increasing intake of foods rich in anti-oxidants, omega-3, micronutrients and dietary fibers (e.g., fruit, vegetables) and the appliance of a gluten free diet. However, data from the available studies were generally graded of low quality and it was noted that placebo and/or nocebo effects influenced the reported positive effects. In addition, such effects were no longer seen when adjusting for confounders such as overweight, when a translation was made from in vitro to in vivo, or when the nutrients were not supplemented as isolated sources but as part of a mixed daily diet. Finally, some studies showed that long-term adherence to a gluten free diet is often associated with an impaired diet quality and nutrient intake, leading to negative health outcomes and reduced QoL. Concluding, scientific evidence on the efficacy of dietary interventions on well-defined clinical endpoints of endometriosis is lacking and recommending a gluten free diet to women solely diagnosed with endometriosis should therefore not be advised.

INTRODUCTION

Endometriosis is characterized by the presence of endometrium-like tissue outside the endometrium and myometrium, usually with an associated inflammatory process [1]. The presence of intra-abdominal endometriosis can be suspected based on clinical symptoms such as dysmenorrhea, dyschezia, hematochezia, dysuria, hematuria, dyspareunia, chronic pelvic pain and infertility. Complaints are often related to the menstrual cycle and may be progressive in nature. Therefore, endometriosis can be associated with reduced mental, physical and social wellbeing leading to a lower quality of life (QoL) [2-4]. Because of this, Saunders and Horne [5] recently proposed to consider endometriosis as a syndrome rather than a single disease state. The QoL impairment, the risk of work-related disability and unemployed work status as well as the related costs are high and similar to other widespread chronic inflammatory conditions such as Diabetes Mellitus Type 2, Crohn's disease and Rheumatoid Arthritis [1,3,6,7].

Because many endometriosis symptoms strongly overlap with other chronic conditions such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and celiac disease (CD) (see Figure 1), early diagnosis is often missed [8-15]. In the Netherlands it may take up to 10 years, with a median delay of 7.4 years between a first visit to a medical practitioner and a confirmed diagnosis of endometriosis [16]. During the period of diagnostic delay, 75% of women consult 1 – 4 medical professionals for their symptoms because they are not satisfied with the advice and/or treatment offered [17]. In general, it can be stated that clinical symptoms and the experience of the patient do not always reflect the severity of the disease [18]. Treatment of endometriosis consists of four pillars: hormonal therapy, pain management, surgery and/or therapy with assisted reproductive techniques (ART). Nevertheless, applied medical and/or surgical treatment methods can be insufficient to alleviate symptoms or may be accompanied with side effects. Both can affect treatment compliance negatively [19-21]. This has resulted in an increasing interest in self-management strategies among women diagnosed with endometriosis [22]. Figure 1.

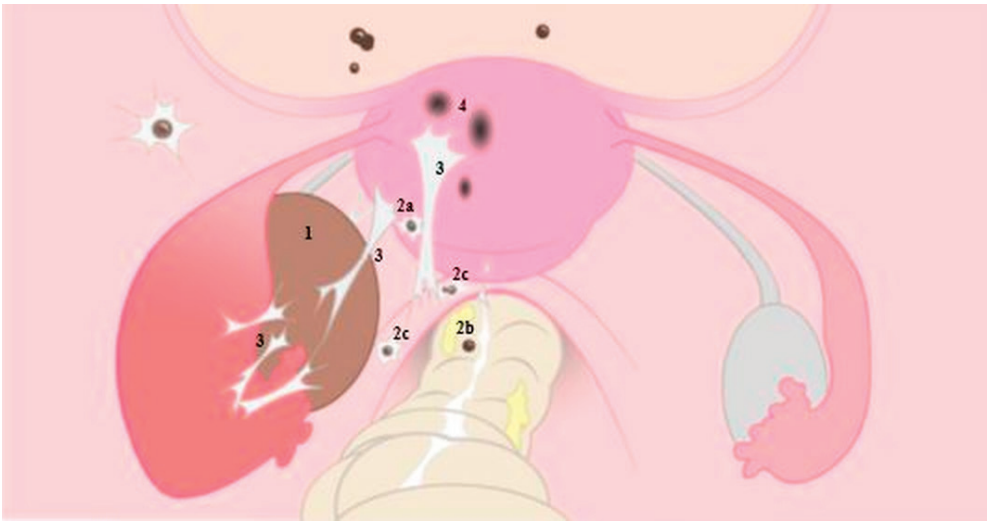

Figure 1. Illustrative representation of endometriosis on the left, with normal anatomy of the female reproductive organ on the right. 1: ovarian endometrioma, 2: deep endometriosis located on the bladder and posterior uterine wall (2a), on the rectal wall (2b) and sacro-uterine ligament (2c), 3: adhesions caused by endometriosis, 4: adenomyosis. With permission L. van der Houwen [23].

Within the realms of complementary and alternative medicine suggestions are being made, i.e. on social media but also in a number of medical publications, that a range of non-medical, often self-management strategies might result in pain relief and an improvement of wellbeing. They include relaxation exercises (e.g., yoga, breathing exercises and meditation), the use of heat, acupuncture, physiotherapy and the use of cannabidiol (CBD) oil. In addition, specific dietary measures such as a gluten free diet (GFD), the Low FODMAP diet and the so-called endometriosis diet (aspects of these are discussed further below in detail) have been suggested to help mitigate endometriosis associated pain and discomfort [1,24-30]. Women that are receptive to suggestions regarding symptom reduction often self-implement such measures [22,26,31-35] and recently it was shown that this may result in positive effects on QoL [36,37]. Because of this, the current European endometriosis guidelines advice healthcare providers to discuss non-medical strategies and address aspects of QoL and psychosocial wellbeing. However, since evidence providing plausible biochemical mechanisms explaining the perceived benefits is scarce or lacking [30] no recommendations are made in these guidelines regarding dietary strategies [1].

Associations between diet components and endometriosis have been addressed in a number of recent systematic analysis and reviews but they do not reflect causality [38-44]. Plausible mechanisms related to the effects of specific food components on pathology and symptoms in vivo, that may underlie these associations, have thus far hardly been discussed thoroughly. Much of the data pointing to plausible mechanisms is obtained from in vitro and animal studies which do not necessarily reflect the human situation.

Therefore, we aim to critically discuss the explaining associations between endometriosis and dietary interventions, and their challenges and limitations. We will do this by the example of three selected diet components. Supplementation with omega 3 fatty acids and red meat avoidance will be discussed in short, whereas the association between gluten related pathologies and endometriosis will be discussed in great detail.

For this narrative overview, selected original research papers were obtained using the university E-Library academic search tools PUBMED, WEB OF SCIENCE, SCOPUS and EMBASE, ENDNOTE global search tool, as well reference lists in research papers and reviews (see Appendix). Papers on randomized controlled trials, retrospective and prospective studies, systematic reviews and meta-analysis were included in this narrative review. Relevant citations in publications were cross-checked with the original content in the sources cited.

ENDOMETRIOSIS BACKGROUND

Prevalence of endometriosis

It is estimated that over 175 million women worldwide suffer from endometriosis and is thought to occur in 5 – 15% in women of reproductive age (15-49 years) [45-50]. With women of reproductive age representing about 38% of the global population, the currently reported endometriosis prevalence equals between 1.9% and 5.7% in the global population [51,52]. Underreporting due to diagnostic complexity and delay is very likely.

Causes and mechanisms associated with endometriosis

Due to the complexity of endometriosis and the multiple associations with other diseases and/or disorders, many hypotheses on endometriosis etiology have been put forward. The most accepted and oldest theory dating back to 1927 is the "Retrograde menstruation" theory, also referred to as the "Implantation Theory". In this theory it is proposed that fragments of the endometrium are dragged through the Fallopian tubes into the abdominal cavity during menstruation, followed by implantation on the peritoneum. These mucosal fragments can form endometriotic lesions which in turn can spread through the abdominal cavity. However, it should be noted that the phenomenon of retrograde menstruation physiologically occurs in the majority of women with patent Fallopian tubes whereas only a fraction of women develop endometriosis [53-55]. Therefore, other theories are proposed including coelomic metaplasia (which has been suggested in women with Mullerian duct defects and explains peritoneal lesions by the transformation of peritoneal mesothelium into glandular endometrium) and hematologic or lymphatic spread (which explains extra-pelvic lesions) [5,21].

The pathogenesis of endometriosis includes local estrogen production, progestogen resistance as well as chronic local and systemic inflammation. An altered inflammatory response, usually mediated by tumor necrosis factor (TNF)-alpha expression and sustained by Interleukin (IL)-16 in the peritoneal cavity, appears to be estrogen-dependent. Post-menarchal increased estrogen levels have been shown to impact endometriosis prevalence, whereas reduced levels are clearly associated with a lower prevalence [56]. In addition, estrogen contributes to the growth and proliferation of endometrial cells, both *in utero* and of ectopic endometriosis lesions. It also suppresses the expression of several anti-inflammatory genes (IL-8, IL-6, TNF-a) and is involved in the modulation of endometriosis-related pain by exerting neuro-modulatory functions, both through indirect and direct mechanisms, on sensory and sympathetic nerves [57]. Suggestions have been put forward that estrogens from meat consumption may contribute to endometriosis risk resulting in recommendations to avoid or limit red meat consumption [58,59]. Finally, another theory concerns Bacterial /microbial contamination and "Dysbiosis[2]" [60-63]. It is suggested that intestinal dysbiosis, for example in celiac disease patients, is associated with inflammation, impaired barrier function and microbial translocation possibly increasing the risk of endometriosis. However, thus far no plausible mechanisms have been defined to explain how dysbiosis could cause endometriosis. Below we discuss this matter in more detail. Extensive recent reviews on endometriosis subtypes, pathogenically mechanisms and etiology pathways are published in recent reviews [5,55,64-67]. An illustrative representation of endometriosis is given in Figure 1.

Critical assessment and discussion on the association and cause-effect of selected dietary factors in endometriosis

Several studies have suggested there might be a causal effect between the development of endometriosis and either supplementation or avoidance of certain supplements and/or nutrients. However, these studies are often of low quality and only show associations. They do not provide proof of causality. Therefore, a number of critical aspects in the assessment of the effect of a diet or specific dietary components on health outcomes are discussed below. Available observational studies have suggested a strong overlap between symptoms associated with endometriosis and with other chronic diseases which are also characterized by immune and inflammatory responses such as CD, ulcerative colitis, Crohn's disease, non-celiac/wheat gluten sensitivity (NCGS/NCWS) and IBS [7,68-72]. In women diagnosed with endometriosis a 2-3fold risk to also be diagnosed with IBS has been observed [38,39]. In women suffering from IBS and being suspect of gluten related symptoms, a 5 to 6-fold risk of suffering from CD was found [73]. Both a case control study [74] and a systematic review and meta-analysis [75] concluded that endometriosis was associated with autoimmune diseases including ID and IBD. However, both authors addressed

2 Dysbiosis is a lasting unfavorable change in the composition/diversity of resident microbiota communities and their metabolism, relative to that found in healthy individuals (60).

there is little understanding of shared biological mechanisms and pathways between endometriosis and autoimmune diseases that would explain such association (Figure 2).

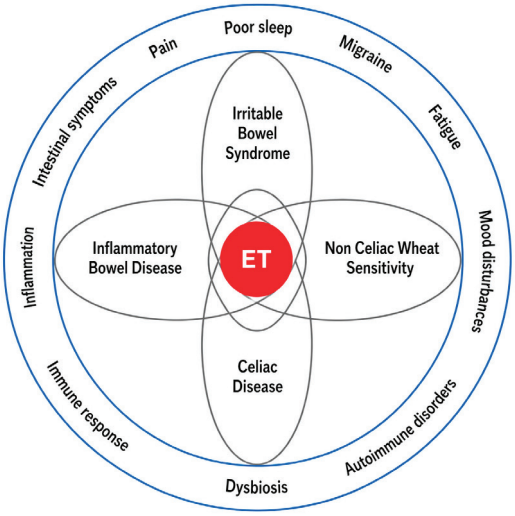

Figure 2. Endometriosis characteristics and symptoms are associated with other disease states, which raises questions about the chance of "shared" underlying pathologies as well as possible risks that one initiates and/or potentiates the other. Since associations are no proof of causality great care should be taken with the interpretation of their meaning.

Because specific food components are involved in the pathologies of CD, ulcerative colitis, Crohn's disease, NCWS and IBS, and because these diseases are thought to be associated with endometriosis, suggestions have been made that nutritional strategies recommended in these conditions might also be relevant for women diagnosed with endometriosis. A few examples of diets suggested to be beneficial for women diagnosed with endometriosis are an anti-inflammatory diet that is rich in long chain poly-unsaturated fatty acids (PUFA) and polyphenols and low in trans-fatty acids [58,76-78]; the Low FODMAP diet (FODMAP - Fermentable Oligo-, Di-, Monosaccharides And Polyols which give rise to gas formation, osmotic fluid shift, feelings of bloating and intestinal distress) [27]; a low nickel diet [79] and finally supplementation with pre-, pro- and synbiotics[3] [80]. In addition, was advised to reduce or avoid red meat consumption (both processed and non-processed) because of its content of heme-iron (a potential pro-oxidant) and a suggested presence of estrogens due to hormonal treatment of cattle. Hormonal treatment of cattle is a farmers practice to stimulate growth and meat yield, in countries where this is legally allowed like the United States. However, it is forbidden in all European countries [58]. The avoidance of red meat is part of the so-called endometriosis diet [37,81]. However, the

3 *Prebiotics: fermentable carbohydrates that are preferably fermented by health beneficial microbiota such as lactobacilli and bifidobacteria. Probiotics: food supplements supplying health beneficial live microbiota. Synbiotics: supplement containing pre- and probiotics.*

extensive analysis of available data performed by Shafrir et al. [82] and by Nap and de Roos [30] concluded that "conflicting results have been reported on the associations between endometriosis and dietary components". Therefore, there is no clear advice regarding dietary interventions in the most recent EHSRE guideline for endometriosis [1,30,82]

Although pain perception may be used as a subjective clinical endpoint it is influenced by many factors, among which also positive and negative expectations, cognitive attention and mood. Nevertheless, patients who self-implement nutritional measures indicate that these result into better wellbeing and less pain perception [28,33,37,40,81,83]. Part of the positive effect of a food component on mood and QoL may be attributed to a placebo effect (a positive effect experienced just because the user thinks that intake of the component helps the condition) or nocebo effect (belief that a negative outcome occurs because a certain food component causes harm and avoiding it will result in feeling better). Both placebo and nocebo effects are based on expectations which are subject to tremendous influence of the news in social and main stream media as well as opinions of peers and health professionals in close contact. The latter was confirmed in a randomized, double blind, placebo-controlled, international multicenter study, addressing the effects of expectancy on experiencing adverse reactions of gluten intake, after exposure to foods labelled "gluten free" or "containing gluten" [84]. It was shown that the combined effect of expectancy had a strong effect on overall and individual GI symptoms, reflecting a nocebo effect. In addition, a recent meta-analysis concluded that evidence of positive impact on pain perception and QoL, was derived from non-randomized controlled trials with small sample sizes. There were multiple sources of bias and when assessed using GRADE criteria the evidence was graded as low to very low-quality [41,85,86]. Nevertheless, despite the presence of placebo/nocebo effects, Leonardi et al. plead to encourage patients and healthcare providers to more strongly consider and encourage diet treatments if this improves the patients' wellbeing, even if these improvements may be induced by effects of expectation and belief [83]. This strategy may bear certain risks because the advised diet treatment might induce changes in nutrient intake. This is important to patient's health and is discussed later in this paper.

ASSOCIATION OR PROVEN CAUSE-EFFECT?

Endometriosis and microbiota

Although the uterus has been considered a sterile environment for a long time, it has recently been found that the endometrium harbors low quantities of resident microbiota [87]. However, much less than in the vagina [88,89]. It has additionally been suggested that fecal compounds and/or microbiota may contaminate the vagina [90] leading to cervico-vaginal dysbiosis, inflammation, infection and tissue damage [91-93]. It has been hypothesized that this deteriorates endometrium integrity, allowing for the migration of cells or tissue

fragments with blood to other sites. It is suggested that the latter may result in tissue adherence and the initiation of endometriosis lesions [94-97]. Similarly, Blander et al. argued that an increase in pro-inflammatory and a decrease in anti-inflammatory microbiota composition may result in conditions leading to increased epithelial permeability, giving rise to microbial infiltration and translocation to blood [984]. This may in turn lead to metabolic inflammatory conditions similar to endometriosis [99,100]. Dysbiosis in CD, NCWS, ulcerative colitis and Crohn's disease is associated with inflammation induced impaired intestinal barrier integrity [101] and may lead to passage of bacteria into blood, evidenced by the presence of flagellin (marker of microbial translocation from intestine to blood) in blood [102]. Because of overlapping inflammatory metabolism and symptoms it has been speculated that endometriosis and intestinal dysbiosis may interact. However, whether intestinal dysbiosis is causal to developing endometriosis is highly speculative and remains unproven.

Intestinal dysbiosis, estrogen cycling and endometriosis

A potential effect of the gut microbiome associated estrobolome - a collection of genes in the intestinal microbiome modulating the amount of resorption of estrogen passing from blood into the intestine - has been described. It was discussed that intestinal dysbiosis may lead to excess estrogens being reabsorbed, causing a hyper-estrogenic environment that will impact endometriosis [63,103,104]. It has been shown that intestinal resident microbiota communities are influenced by hormonal changes, which behave cyclical. In addition, hormonal fluctuations can modulate anti-microbial peptides in the uterine mucosa and endometrial fluid, as well as influence the local endometriosis immune cells [105,106]. Thus, both the endometrium microbiome composition and the way its metabolism is changed by hormonal cycling and vice versa may theoretically play a role in endometriosis etiology.

Perrotta et al. determined the fecal microbiota composition by collecting rectal swabs of women with and without endometriosis. They found no differences in fecal microbiome composition of endometriosis patients versus their healthy controls [107]. However, experimental animal studies suggest that the intestinal microbiota may lead to endometriosis and disease progression. Chadchan et al. observed that antibiotic treatment in an experimental endometriosis mouse model reduced inflammatory markers and endometriosis progression [108]. An influencing role of intestinal microbiota related metabolism and/or endotoxemia is a likely explanation. Ni et al. observed that microbiota induced changes in fecal matter of experimental endometriosis mice (increased bile acid and decreased alpha-linolenic acid concentration) were related to disease progression [109]. However, in this study dysbiosis and related metabolic effects occurred after the mice were treated

4 *Microbial translocation is defined as the passage of both viable and nonviable microbes and microbial products such as endotoxin, across an anatomically intact intestinal barrier (100).*

with estrogen and endometrial fragments were transplanted. Therefore, the conclusion that dysbiosis was causal to endometriosis development by Ni et al. [109] seems unjustified. How the introduction of endometriosis in these mice has resulted in the initiation of dysbiosis remains unclear. It has been shown that diet and microbiota related increased β-glucuronidase activity can result in elevated estrogens levels whereas a dysbiosis induced decreased activity may induce decreased circulating estrogens [110], which in fact should counteract the earlier suggested positive association between dysbiosis and endometriosis. Neither dysbiosis nor dysbiosis-associated effects on estrobolome, while suggesting that these pose an increasing the risk of endometriosis, should be an argument to avoid gluten. At present, there are no in vivo cause-effect data in this respect.

As mentioned above, many associations between the consumption of certain food components and occurrence of disease symptoms are based on observational data showing correlations. However, this does not provide proof of causality. In addition, favorable effects observed after exposure to isolated food components in *in vitro* and in animal intervention studies do not allow direct generalization to daily human mixed diet consumption conditions. Another critical aspect is how well all factors that play a role *in vivo* are truly comparable to the increasingly performed *in vitro* tests. Oral food processing, gastric peristalsis, intestinal transit, the presence of digestion enzymes and organic acids in oral cavity, stomach and intestine (carbohydrases, proteases, gastric acid and bile) as well as the processes of absorption (transport mechanisms) that play a large role in *in vivo* studies, should be similar to the circumstances of *in vitro* studies. However, *in vitro* systems lack feedback from the gastrointestinal sensors in delaying gastric emptying and extending gastric acid exposure. They additionally lack a mucus layer, delaying exposure to the enterocytes for absorption, while at the same time extending intraluminal digestion. In addition, with the exception of organoids, they lack brush border membrane-associated enzyme activities which can influence the rate of digestion and absorption [111,112].

Another point of concern is that the direct *in vitro* exposure of bioactive molecules to cells or cell-lines are often unrealistic with respect to the *in vivo* situation. The quantitative exposure (bio-accessibility) and the resulting bioavailability may be extremely low *in vivo*. In addition, the test molecules may undergo microbial modification in the intestine prior to absorption. For example, as a result of microbial metabolism, pro-inflammatory and immune stimulating compounds, e.g. conversion of primary to secondary bile acids [113,114] , and alternatively, anti-inflammatory compounds (e.g. derived from antioxidant-polyphenols) [115] may be formed in the intestine. In addition, post-absorption, many of the absorbed compounds will also become subject to conjugation in the liver, which changes their potential bioactivity and health effects. For this reason, total antioxidant capacity, as measured *in vitro,* has no relevance for the *in vivo* situation and its use as "favorable for health" should be discouraged [116].

Effects of isolated food components vs. mixed diet on endometriosis

Effects of isolated food compounds, as observed in *in vitro* studies, may differ from effects when it is part of a mixed diet. As an example, it was long assumed that free radicals present in cigarette smoke cause oxidative stress in the lungs, and that this plays a role in the development of lung cancer. Based on *in* vitro data it was thought that supplementing lipophilic antioxidants such as vitamin E and carotenoids would counteract oxidative stress and decrease lung cancer risk. However, a higher lung cancer incidence and deaths among consumers taking beta-carotene supplements, compared to the placebo group [117,118]. Positive effects of fruit and vegetable consumption on the risk of developing endometriosis have been suggested because these are rich in antioxidants, micronutrients and dietary fibers [81,82]. However, the observational study by Schwarz et al. (113) drew a contradictory conclusion. After adjusting for a healthy eating index, positive effects associated with fruit fibers disappeared. Even more so, when pooling total vegetable and cruciferous fiber intake an increased endometriosis risk was observed [119]. A recent systematic review by Nirgianakis et al. [42] reviewed 9 human and 12 animal studies addressing the effect of dietary interventions on endometriosis. The human studies were classified as supplementation with isolated dietary components (e.g., antioxidants), exclusion or avoidance of selected dietary components (e.g., red meat), or complete diet modification. It was concluded that although the selected animal studies showed promising results, they did not reflect the reality of consumption in humans [42]. Accordingly, before making recommendations, effects observed *in vitro* or in animal model studies should always be confirmed by human intervention studies with habitual frequencies and quantities of food intake. Below we aim to put this complexity further in perspective by discussing two specific examples of diet components which, based on experimental data in animals, *in vitro* studies, as well as observational data, are suggested to play a role in endometriosis etiology and/or symptoms, but lack a clear cause-effect evidence: (1) omega-3 fatty acids and (2) red meat. Subsequently, dietary gluten will be discussed in great detail.

Omega-3 fatty acids

It has originally been suggested that omega 3 poly-unsaturated fatty acids [n-3 PUFA: α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], as precursors of prostaglandins, express anti-inflammatory activity [120]. Observational data show that low fish oil consumption is associated with a 22% more likelihood to be diagnosed with endometriosis [77]. Based on this observation supplementation is often advised to patients suffering from inflammatory diseases such as rheumatoid arthritis, IBS, IBD but also endometriosis. However, the question is whether there is a plausible mechanism by which n-3 PUFA may either reduce endometriosis initiation or endometriosis associated symptoms.

Supporting that the effects of a single food component may differ from the effect of the component when being part of a mixed diet, studies have shown that the effects

of n-3 PUFA supplementation may differ for consuming fatty fish as a source of omega 3. Observational study outcomes are conflicting (50, 120, 124), the biological plausibility is lacking and there is debate on the efficacy to reduce inflammation *in vivo* [43,121-124]. Su et al. performed a meta-analysis and concluded that there was no benefit of ALA on reducing blood inflammatory markers [44]. In contrast, they surprisingly found that ALA supplementation may increase inflammation. Nodler et al. [125] performed a double-blind placebo-controlled study on the effects of n-3 PUFA supplementation for 6 months in adolescent girls and young women with endometriosis. Increased n-3 PUFA intake resulted in a reduction in pain scores not different from placebo treatment. It is discussed that "*caution must be applied given the widespread direct marketing of these supplements to girls and women with endometriosis implying a beneficial impact on symptoms. A strong placebo effect was evident in multiple outcome measures, suggesting that participation itself, and not the supplements, conferred improvement even at six months*" [125]. Despite the observed association between higher levels of fish oil consumption and reduced endometriosis risk [77], evidence to conclude that n-3 PUFA supplementation causally helps to reduce endometriosis initiation or symptoms is lacking. The differing results discussed above reflect that the overall composition of the diet (including other factors influencing inflammatory or anti-inflammatory potential) plays a critical role. In addition, the physical condition of the individual (presence of obesity, associated decreased microbiota diversity and presence of insulin resistance) as well as smoking behavior will also influence the effects of diet and of study outcomes [126].

Red meat

A prospective cohort study by Yamamoto et al. investigated the effect of meat consumption on endometriosis risk and found a positive association. They suggested that this may at least partially be caused by heme-iron (acting as pro-oxidant, inflammation inducer) and steroid hormones present in meat. However, other studies did not confirm these findings and suggested that this may only occur when consuming seven or more red meat servings per week, which, with habitual food consumption may only happen in extreme cases [127]. These contradicting findings require a critical assessment of potential sources of bias that may influence data interpretation. For example, high meat consumers generally are overweight [128], which is associated with low-grade chronic inflammation [129]. Montonen et al. noted that an elevation of inflammation markers (hs-CRP) in high meat consumers was no longer significant after adjusting for overweight [130]. In addition, obesity in women, in particular abdominal obesity, is associated with elevated serum and adipose tissue estradiol levels [131-134]. It is possible that the effect observed by Yamamoto et al. was due to overweight, which they did not correct for in their analysis [58]. Furthermore, Yamamoto et al. referred to other studies suggesting that hormones from steroid hormone-treated animals, present in consumption meat, may play a role in endometriosis risk [58,135,136]. However, the cited study of Andersson and Skakkebaek (131) concerned pre-pubertal young children whereas in the other study Brinkman et al. (132) studied

postmenopausal women. In both cases endogenous estrogen production was low. It is thought that the impact of estrogens from meat consumption on circulating estrogen levels will differ much from that in women of reproductive age, because they have a much higher endogenous estrogen level [136]. Concluding, none of the studies available at present quantified estrogen levels in meat (and as a result of consumption) and there is no conclusive data that (red) meat consumption is causally involved in endometriosis etiology and symptomatology.

DO ADVERSE EVENTS OF GLUTEN INTERACT WITH ENDOMETRIOSIS?

Both untreated (newly diagnosed) celiac disease and confirmed endometriosis are associated with inflammation, immune responses and dysbiosis. This raises the question whether other disease states showing similar and overlapping associations may mutually and interactively worsen endometriosis pathology. For example, is it plausible that inflammation and immune response signaling molecules released from intestinal sites due to gluten exposure potentiate inflammation of endometriosis lesions at other sites? To put this matter in a correct perspective, background of gluten, gluten related pathologies and effects of GFD are discussed step by step below.

What is gluten?

The main storage proteins of all cereal grains, with the exception of oats and rice, are "prolamins". This term is based on the fact that these proteins are rich in proline and glutamine. Gluten is comprised of two prolamin fractions, gliadin and glutenin. Figure 3 represents an approximate composition of wheat and wheat protein. Glutenin is particularly important for the formation of an elastic network during dough kneading, subsequently enabling the entrapment of fermentation gases and rising of the dough. Gliadin is the more important fragment, arising from protein digestion (peptides), that can cause adverse reactions in the intestines (see further below). Gluten contributes to about 70 – 80% of the total grain protein content in common (bread) wheat, ~78% in spelt wheat, ~70% in emmer wheat (all 3 used in bread making) and ~77%, in durum wheat (mostly used for pasta making) [137,138].

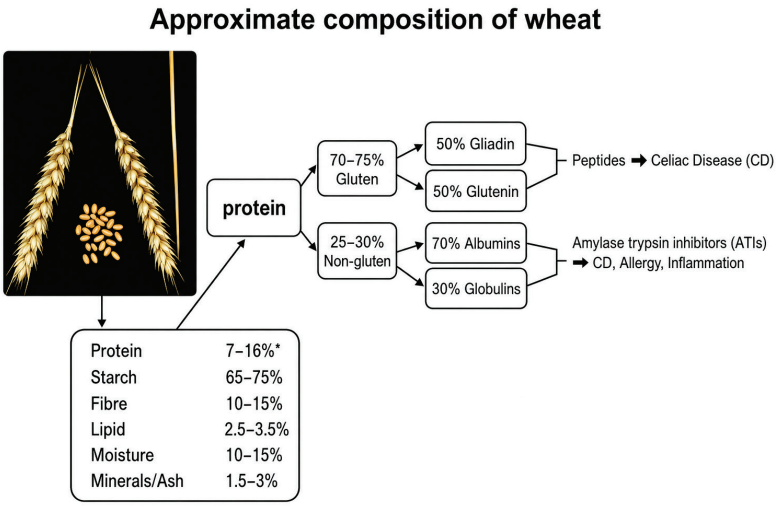

Figure 3. Composition of the wheat kernel and of wheat protein, based on data from (138, 139), adapted from Brouns and Shewry (2022).

Based on the measurement of "true ileal digestibility" it has been suggested that the degree of digestion of wheat protein in humans is »90-95%, similar to the range of digestion of most plant proteins [139]. Specific sections of the gluten protein contain proline-rich sequences which cannot be degraded by the human proteases pepsin, trypsin and chymotrypsin. This results in a small fraction of peptides that potentially may cause immune and inflammatory responses in the intestines in susceptible individuals (see next section for detail). The storage proteins in barley (hordein, ~50-55% of total protein) and in rye (secalin, ~47-50%) are molecular closely related to gluten and are therefore considered as "gluten proteins" [137,140]. Because avenin proteins in oats do not resemble gluten, oat is generally considered to be a gluten free grain. However, oat-based foods may become contaminated with gluten containing grains or flours in the agri-food chain. In social media it is often suggested that ancient wheat types contain less gluten and are safer for individuals suffering from gluten disorders. However, an extensive compositional analysis of wheat types showed that over time the protein content slightly declined while starch content increased. Similar to these observations, recent analysis showed that the "ancient" wheat types spelt, emmer and einkorn have higher contents of gluten compared to common wheat (bread wheat) [138]. Along with the higher protein content, the amount of gliadin and digestion resistant gliadin derived immuno-reactive peptides involved in the etiology of celiac disease is also higher in these wheats [138,141-143].

Gluten disorders pathology and prevalence

Undigested gluten peptides (size of 10-40 amino acid residues), exposed to the intestinal epithelium, can pass the luminal side of intestinal epithelium and enter the lamina

propria via the transcellular or paracellular route. Subsequently, peptide deamidation by the enzyme "tissue transglutaminase" (tTG) takes place. In addition, dendritic cells recognize specific amino acid sequences on the surface of the antigen (called epitopes) which can lead to binding to HLA-DQ2 and HLA-DQ8 molecules on antigen-presenting cells and subsequent initiation of immune and inflammatory responses [144]. This condition ultimately leads to increased numbers of intraepithelial lymphocytes and villous damage. The latter causes digestion-absorption problems that are found in up to 38% of patients with CD, where one or more nutritional deficiencies (calories, dietary fiber, vitamins and minerals) are seen. This might result in diarrhea, steatorrhea and weight loss [145,146]. Extensive detail on CD etiology and pathology can be found in other reviews [69,147,148]. Different features of gluten/wheat exposure in CD, wheat allergy (WA) NCWS and of endometriosis are presented in Table 1.

Important to notice is that CD only develops in genetically predisposed individuals, expressing the gene haplotypes HLA-DQ2 or DQ8 [151,152]. Approximately 25 – 40% of the general population (the exact numbers differ per country that was studied) is predisposed and expresses these gene haplotypes [153,154]. However, based on confirmed diagnosis it is estimated that only about 4-6% of these predisposed individuals actually develop CD. A global mean population prevalence of about 1% is mostly cited. The fact that the majority of predisposed individuals do not develop CD implies that additional environmental non-gluten factors might play a role in the disease initiation [155].

Table 1. Features of gluten/wheat exposure in celiac disease (CD), wheat allergy (WA), non-celiac wheat sensitivity (NCWS), formally often named non-celiac gluten sensitivity (NCGS) and of endometriosis. Abbreviations: GI, gastrointestinal; GS, gluten sensitivity; IEL, intraepithelial lymphocytes.

	CD	**WA**	**NCWS**	**Endometriosis**
Prevalence	1-2%, Global mean ~1%, more in women than in men (ratio 2:1 to 3:1).	0.25% in global population	0.5-10% ? in global population	5-15% in reproductive women, 1.9 – 5.7% global population
Time interval between gluten/ wheat exposure and onset of symptoms	Weeks - years	Minutes - hours	Hours - days	Unclear
Pathogenesis	Autoimmunity (innate and adaptive immunity)	Allergic immune response	Innate immunity	Unclear
HLA	HLA-DQ2/8 restricted (~97% positive cases)	Not HLA-DQ2/8 restricted (35-40% positive cases as in the general population)	Not HLA-DQ2/8 restricted (50% DQ2/8-positive cases)	Not HLA-DQ2/8 restricted No data available in endometriosis patients [149]

Table 1. (*continued*)

	CD	WA	NCWS	Endometriosis
Autoantibodies	Almost always present	Always absent	Always absent	Present, HLA class 2 system may be involved in etiology [150]
Enteropathy	Almost always present	Always absent (eosinophils lamina propria)	Always absent (slight increase in IEL)	Often present
Symptoms	Both intestinal and extra-intestinal (not distinguishable between these three gluten-related disorders). Common intestinal symptoms: bloating, abdominal pain, diarrhea, nausea, epigastric pain, alternating bowel habits, dysbiosis, inflammation. Common extra-intestinal symptoms: lack of wellbeing, tiredness, headache, anxiety, foggy mind, impaire quaity of life.			Strong overlap with gluten associated adverse reactions
Complications	Co-morbidities, longterm complications	Absence of co-morbidities, short-term complications (including anaphylaxis)	Absence of co-morbidities and long-term complications (long follow-up studies needed to confirm this)	Co-morbidities, long-term complications

The prevalence of CD in the global population is about 1-2%. Santoro et al. observed CD in 5 (2.2%) out of 223 women with confirmed endometriosis whereas only 2 cases of CD were found in the 246 control subjects (0.8%) [156]. In addition, Aguiar et al. observed a CD prevalence of 2.5% in a cohort of 120 women with laparoscopically confirmed endometriosis, compared to a prevalence of 0.66% in their control group [157]. Based on these observations one may conclude that the actual prevalence of CD among endometriosis patients is only slightly higher than in the general population. Finally, the largest survey thus far was performed in Sweden [158]. In this study, using biopsy reports from all Swedish pathology departments, 11 097 women with confirmed CD were identified. None of them had a diagnosis of endometriosis before study entry. These patients were matched with data of 54 992 controls not suffering from CD. All individuals were followed up for a period of at least 5 years. During this period 118 individuals with CD and 399 matched controls developed endometriosis. When restricted to women of reproductive age at study entry (16–45 years), the mean increased risk was 35% (HR 1.35; 95% CI. 1.07–1.69). The authors concluded that endometriosis seems to be associated with previously diagnosed CD. Potential explanations included shared etiological factors and CD-mediated inflammation. How intestinal inflammation would cause initiation of endometriosis remains unclear. However, contrary to previous beliefs, in a recent study by Schwartz et al (134), gluten intake was associated with a significantly lower risk of endometriosis diagnosis. Although an explanation for this inverse association was unclear,

the results provided some evidence that eating gluten-containing foods did not increase risk of endometriosis diagnosis.

A reason often cited for recommending a GFD to endometriosis patients is the study conducted by Marziali et al. [26]. They reported that endometriosis symptoms decreased after 12 months of adherence to a GFD. An important aspect of this study is that none of the patients had been tested for CD when being enrolled in the study. When suffering from CD, a GFD will reduce inflammation and immune response related symptoms, which are known to overlap with endometriosis-related symptoms. It may be that individuals showing improvement of symptoms were, at least partly, undiagnosed CD patients. In addition, 2 weeks after starting a GFD, 88 study participants had withdrawn because of side effects caused by a GFD, such as abdominal symptoms due to other food intolerances (which were not specified). Only the 207 patients who showed improvement of symptoms were allowed to continue the study. This approach may have caused undesired skewing into the direction of the favorable effects of a GFD on endometriosis-related symptoms which were seen in 156 participants whereas 51 participants showed no effect. In addition, based on similar effects seen in patients suffering from gluten/wheat sensitivity, as discussed above, strong nocebo effects related to gluten intake and placebo effects due to avoidance of gluten may have been present. Recently it was shown that, compared to non-patients, women suffering from endometriosis were more likely to self-implement a GFD, similar to observations in patients with IBS. In addition, it was six times more likely that women who implemented a GFD also made other dietary changes in the past years [159]. An overview observed associations between gluten, CD and endometriosis is given in Table 2.

Table 2. Observed associations between gluten, celiac disease (CD) and endometriosis.

Author	Year	Ref	Main finding	Mechanism
Aguiar et al.	2009	178	CD in 2.5% in of women with laparoscopy confirmed endometriosis, vs. 0.66% in control group	unclear
Stephansson et al.	2011	179	In women of reproductive age having CD the mean increased risk of developing endometriosis was 35%	unclear
Marziali et al.	2012	25	Endometriosis symptoms decreased significantly after 12 months gluten free diet	unclear
Caserta et al.	2014	205	Case report emphasizing the possible association between CD, endometriosis and infertility	unclear
Santoro et al.	2014	177	CD in 2.2% out of women with confirmed endometriosis vs. 0.8% in control group	unclear

Table 2. Observed associations between gluten, celiac disease (CD) and endometriosis. (*continued*)

Author	Year	Ref	Main finding	Mechanism
Schwartz et al.	2022	134	Gluten intake is associated with a significantly lower risk of endometriosis diagnosis	unclear

Is dysbiosis in celiac disease a cause or a consequence of the disease?

Zafeiropoulou et al. showed that the presence of specific bacteria was CD dependent despite the fact that adherence to a GFD had altered intestinal microbiota composition [160]. Recently it was shown that the abundance of several species, pathways and metabolites was altered at the time of CD diagnosis, characterized by complex patterns of increased pro-inflammatory species and decreased protective/anti-inflammatory species [161]. El Mouzan et al. studied 40 children with newly diagnosed CD, 20 healthy controls, and 19 non-CD controls. They observed a significant difference in fecal microbial composition of the CD children, among which increased *Bacteroides* and decreased *Lactobacillus* genus counts [162]. Palmieri et al. collected fecal specimens from 46 CD individuals following a GFD for at least 2 years and 30 specimens from healthy controls. The microbial composition of the CD subjects was decreased in *Bifidobacterium longum* genus and several species belonging to the *Lachnospiraceae* family. Also, *Bacteroides* genus was found to be more abundant.

In contrast to other suggestions, microbial profiles of the CD patients were consistently "non-dysbiotic" [163]. After a systematic review of cross-sectional studies by Kaliciak et al. it was concluded that due to a lack of taxonomic uniformity between studies and the enormous inter-individual differences in microbiota composition, a comparison of microbial communities between CD patients, CD-GFD patients and untreated CD patients was impossible [164]. Vacca et al. came to a similar conclusion [165]. These recent observations suggest that unfavorable intestinal microbiota changes and associated metabolism can result from various environmental conditions preceding the diagnosis of CD. Examples of these are self-implemented measures to help alleviate experienced gastrointestinal discomfort and pain (e.g., FODMAP avoidance resulting in low fiber intake, GFD, use of nonsteroidal anti-inflammatory drugs and of antibiotics). Although by adhering to a GFD a partial normalization may occur, the effects of GFD on microbiota changes will not only depend on the avoidance of gluten but also significantly on the compositional quality of the GFD (see further below for more detail).

Non celiac gluten sensitivity

When hearing or reading from influencers and celebrities on social media that gluten in general can cause health-related harm, one may impose a self-belief that gluten is the cause of a range of intestinal symptoms and general malaise and that these symptoms will disappear after adhering to a GFD. This, as well as associated gluten-free market-

ing claims, have led to an increasing belief that 'living gluten-free' is equal to a healthy lifestyle [166]. Within the general population the prevalence of individuals believing that gluten causes harm, resulting in them avoiding gluten, may range from a few percent up to 15% of the general population [166-168]. However, the actual number of individuals having symptoms after consuming gluten or wheat containing foods, while not suffering from CD, wheat allergy or dermatitis herpetiformis, appear to be much lower. For example, Capannolo et al. studied 392 persons (307 females and 85 males) selected from an IBS cohort. They had contacted the gastro-enterology unit because they experienced gastrointestinal symptoms, particularly after consuming gluten. During their initial CD screening, it was found that the positive predictive value of the gluten-related symptoms (defined as the probability that someone with symptoms actually suffers due to gluten/wheat exposure) was only 7% [73]. To put the latter in a correct prevalence perspective, 7% of an IBS cohort (usually representing 10-12% of total population) would equal a NCWS prevalence of close to 1% in the total population. Molina-Infante and Caroccio analyzed data from 10 double-blind, placebo-controlled, gluten-challenge trials, covering data from 1,312 adults. They observed gluten specific effects in 38 of 231 self-reported NCWS patients, confirming the low prevalence of proven gluten/wheat disorders in people reporting symptoms after gluten/wheat consumption. In addition, a 40% rate of nocebo effects was observed [169]. However, it should be noted that the percentage of individuals who were newly diagnosed to suffer from CD during the initial study patient entry screening was 6.63% in the study of Capannolo et al. [73]. This percentage is much higher than the general population prevalence of about 1% and warrants diagnosis to confirm or reject the presence of CD in both IBS and endometriosis patients.

Effects of non-gluten compounds on symptoms overlapping with endometriosis

In studies applying challenge tests with gluten or FODMAP it was observed that individuals with self-reported gluten sensitivity reacted primarily to the rapidly fermentable fructans present in grains. Not gluten but fermentation of FODMAP was found to be a significant trigger of IBS and NCWS symptoms that showed an overlap with endometriosis symptoms [170-172]. Crawley et al. performed a double-blind placebo-controlled gluten-food challenge with equal cross-over, in a population cohort of 1 266 participants (aged 15–21 years). They studied participants who reported gluten induced gastrointestinal symptoms, as indicated by self-reported questionnaires. They found that, compared to placebo, adding gluten to the diet neither induced gastrointestinal symptoms nor worsened mental health. A high nocebo effect was noted. In fact, their gastrointestinal symptoms reported were similar to IBS symptoms which may be caused by multiple factors [172]. These findings do not exclude the possibility that a small subset of individuals reporting sensitivity to gluten/wheat may suffer from an intestinal non-classical type of food allergy (not associated with immunoglobulin E). In this condition, systemic immune activation and compromised intestinal epithelial barrier integrity have been found [102,173].

It is thought that amylase trypsine inhibitors (ATIs), present in wheat and in commercially used wheat gluten isolate, may play a crucial role here [174-176].

SPECIFIC DIETARY MEASURES AND THEIR POTENTIAL CONSEQUENCES

Gluten free diet

Following a life-long GFD is challenging, costly and can be socially isolating. Children and adults with CD report reduced QoL because of the lifelong dietary restrictions [177]. The availability of gluten free food (all food without wheat, barley, rye and for food production technological reasons added gluten isolate) is still very limited. In addition, commercial gluten free food is often of doubtful composition. The use of flours from corn, rice, potato and tapioca, in exchange for gluten containing sources, results in a reduced content of micronutrients, dietary fiber and protein and a higher glycemic response. In addition, there is a higher use of saturated fat, trans-fat and salt in the processing of gluten free foods [146,178,179] and often gluten free labeled foods do still contain significant amounts of gluten [180,181]. A low dietary fiber intake is of particular concern [146] because it will minimize fiber fermenting microbiota diversity (in particular those from *Bifidobacterium* and *Lactobacillus* genera [182]) and metabolism which play a key role in immunity and health [163]. Based on a population-based study with 124 447 participants, Littlejohns et al. concluded that GFD followers have a poorer self-reported health and a higher prevalence of blood and immune disorders and undesired digestive conditions [159]. Because adherence to a GFD and/or FODMAP diet has potential risks of low fiber intakes, special attention to educate and guide endometriosis patients to help select appropriate fiber rich foods is needed. For extensive reviews of these aspects see [183-185].

Low FODMAP diet

For patients suffering from IBS and other diseases associated with IBS-like symptoms it is often recommended to reduce the consumption of FODMAP. Within this category of rapidly fermentable carbohydrates, fructans present in grain-based foods such as bread may lead to a significant daily FODMAP intake [186]. However, the recommendation to avoid these may result in an important reduction of overall fiber intake, unless compensated by consumption of other high fiber sources [187]. It has been shown that chronic low intake of soluble, well-fermentable fiber (diet low in plant-based foods) is associated with small intestinal and colonic microbiome disturbances, decreased intestinal mucus layer thickness and impaired barrier function/increased permeability. This is based both on a study where a gnotobiotic mouse model where mice were colonized with synthetic human intestinal microbiota was applied and an extensive systematic review including only human studies [188,189]. More importantly, low fiber intake causes a reduced saccharolytic fermentation in the colon, resulting in low production of short chain fatty acids

(SCFA) - most importantly butyrate, propionate and acetate. These SCFA are essential for immunity and health protection of the intestine. A reduced SCFA production is known as a pro-inflammatory condition and is associated with an increased risk of IBD, intestinal cancer, reduced insulin sensitivity, intestinal tract associated immune compatibility, impaired intestinal barrier function and/or enhanced permeability. In addition, during reduction of saccharolytic fermentation, an increased protein fermentation and formation of hydrogen sulfide, ammonia, and *p*-cresol and branched-chain fatty acids takes place. These changes are known to promote intestinal inflammation and are also implicated in the etiology of intestinal cancers [190,191]. Hill et al. concluded that a low FODMAP strategy should be implemented with care due to the psychological and nutritional risks of a restrictive diet [192]. Before recommending a complex and restrictive diet, such as the low FODMAP diet or a GFD, a positive medical diagnosis is a must [193,194]. When in post diagnostic guidance the patient is properly educated and guided long-term by nutrition experts, these risks can be minimized [195].

LIMITATIONS OF AVAILABLE STUDIES

Currently available systematic reviews and meta-analyses were all done in the same period (2020-2021), thus considered to have the same available database. In general study outcomes presented and discussed in these reviews showed positive, negative or no associations between the consumption of certain foods and/or nutrients and prevalence of endometriosis, or the perception of pain and QoL. Most intervention studies were of relatively short duration, did not have appropriate control conditions, were subject to significant bias and resulted in low to very low scores of evidence quality. The latter was also concluded in systematic reviews of observational data. As a result, interpretations about the effects of specific foods and/or food components on endometriosis were equivocal [126,127,130,140]. More recently, Nap and the Roos concluded in their critical review that evidence regarding the efficacy of dietary interventions in women with endometriosis is conflicting and effects of dietary interventions on specific types of endometriosis (e.g., superficial peritoneal endometriosis, ovarian endometrioma and deep infiltrating endometriosis) remains unknown. In addition, it is conceivable that certain co-morbidities (e.g., obesity) may also influence the effect of dietary interventions. Moreover, they stated that evidence regarding plausible biochemical mechanisms, resulting in the perceived effects of the dietary intervention, is scarce or lacking (29). As result, it is impossible to make evidence-based recommendations for dietary measures at present, to help reduce the initiation of endometriosis and its management once diagnosed. Current healthy eating guidelines, which include avoiding trans fatty acids, limiting alcohol, meat and salt consumption should also be followed by endometriosis patients (see further below). According to the conclusions presented in Table 3 there seems to be consensus that there is a clear need for better quality studies.

Table 3. Conclusions and recommendations related to moderate-high risks of bias and low to very low-quality evidence in observational and intervention studies evaluated in systematic reviews/ meta-analysis.

Author	Year	Ref	Conclusions and recommendations
Helbig et al.	2020	86	Analysed 19 studies. Results currently available do not permit a clear, scientific recommendation or indicate a detailed diet. To be able to derive more concrete recommendations, we require further studies to investigate the influence of nutrition on endometriosis.
Huijs et al.	2020	40	Study (n=12) quality, including risk of bias, was assessed using GRADE criteria and all were of low to very low quality. Future studies are necessary to gain evidence about which food products are effective and in which amounts.
Nirgianakis et al.	2020	42	All animal (n=12) and human (n=9) studies analyzed were characterized by moderate and/or high-risk bias limiting the validity of the results. More and higher quality original studies are urgently needed to enable safe conclusions on this topic
Osmanlioglu et al.	2021	87	Analyzed 25 human studies and 7 animal studies. Due to the limited size of the samples significance of the association between diet and endometriosis is not conclusive. (grading of evidence quality was not presented). Further research is needed to better identify the role of diet on endometriosis.

Qualitative dietary guidelines for endometriosis patients

A regular consumption of whole grain foods is strongly associated with significant reductions in the risks of diabetes, cardiovascular disease, intestinal inflammatory disorders, intestinal dysbiosis, colon cancer as well as a more favorable weight management. The quantity of dietary fibers and associated bioactive molecules play an important role in this [100,196-207]. These observations have resulted in a globally supported recommendation of food authorities to regularly consume whole grains as part of a healthy diet and lifestyle. Accordingly, there are good reasons to advise the consumption of grains (most of which do contain gluten and FODMAP) to endometriosis patients when there is no diagnosis of biopsy-proven gluten disorders and/or IBS-related FODMAP fermentation distress. In general, women with endometriosis should be recommended to follow the qualitative dietary guidelines as advised by the World Health Organisation (WHO), encompassing restriction of salt, red and processed meat products, reduction of added sugars, syrups and refined carbohydrate/starch sources. In addition, regular intake of whole grains, fruits/vegetables, choice of fat sources rich in mono/poly-unsaturated fatty acids and a reduction of foods containing trans fatty acids [204,208-211]. These recommendations are associated with reduced diet related inflammation and significant reductions in chronic disease. Education of endometriosis patients in this respect will help to avoid implementation of self-treatment strategies, some of which in long term may result in negative health outcomes, particularly when not professionally guided.

CONCLUSIONS

Endometriosis is a multifactorial disorder of still largely unknown etiology. Many etiological and causality hypotheses have been put forward. Yet, none of these give a satisfying full evidence-based explanation for the various manifestations of the disease. A role of nutrition related metabolic, inflammatory and immune factors has been proposed to play a role in the etiology and the symptomatology but this is largely based on assumptions rather than good quality evidence. Endometriosis can be associated with multiple symptoms that strongly overlap with those of CD, Crohn's Disease, NCWS and IBS. They typically share common pathological factors such as inflammation, immune responses, microbiota dysbiosis and impaired epithelial barrier function. In addition, chronic symptoms of poor sleep, chronic fatigue, changed mood, anxiety, migraine and depression are encountered. This, in addition to high recurrence rates, often lead to patient treatment unsatisfaction and the search for alternative, non-medical strategies to help relief symptoms. Among these are diet related recommendations with the target to help reduce inflammation and pain. Patients reported that by applying dietary interventions, they felt better and their QoL improved. However, a careful and critical analysis of the scientific evidence regarding the observed positive effect of dietary interventions on symptoms and QoL points to a strong influence of placebo and nocebo effects. Observational data linking diet factors to the risk of endometriosis are conflicting and form no evidence of causality. Effects of nutrients and/or food components largely depend on molecular characteristics, which may differ significantly within a certain class. The generalizing that a certain class, e.g. "dietary antioxidants", helps reduce oxidative stress and inflammation, and is therefore beneficial to reduce endometriosis symptoms, remains unproven.

Claims that the inclusion or exclusion of certain nutritional components is beneficial for endometriosis prevention and management are largely based on data from experimental *in vitro* or animal studies that suggest positive effects. However, these do generally not reflect habitual diet practices and could be misleading.

There is currently no data available of longer-term nutritional intervention studies using established biomarkers of well-defined clinical endpoints of pathology and symptoms. The fact that grains containing gluten, ATIs and FODMAP are involved in the etiology of CD, NCWS and WA, of which symptomatology and a number of pathological factors overlap with endometriosis, does not provide evidence of a causal role in endometriosis etiology. In addition, there is no convincing evidence that the prevalence of CD, NCWS or IBS is increased in endometriosis patients. Given the potential impact that adhering to a life-long GFD may have on QoL, nutritional status, intestinal microbiota composition and potentially health, a GFD recommendation to endometriosis patients should be discouraged, unless a patient has been tested and positively diagnosed to suffer also from a gluten related disorder.

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Chapter 11

General discussion and recommendations for future research

GENERAL DISCUSSION

With this thesis, we aimed to optimize pain and anxiety management in the infertile patient and (chronic) endometriosis patient and achieve national consensus on a step-by-step guideline for pain management in endometriosis. In Part I we collected all data on the effectiveness of Virtual Reality (VR) during outpatient benign gynaecological procedures and applied VR during hysterosalpingography (HSG) and Assisted Reproductive Therapy (ART), all with the aim of reducing procedural pain and anxiety. Part II aimed to create a step-by-step guideline for pain management for the endometriosis patient and study a new development for managing endometriosis-related, visceral pain and optimizing quality of life (QoL): Spinal Cord Stimulation (SCS). Finally, Part III studied the effect of dietary interventions on endometriosis-related pain and QoL as part of self-management.

PART I: PAIN AND ANXIETY MANAGEMENT USING VIRTUAL REALITY IN THE INFERTILE PATIENT

Despite efforts to provide optimal pain and anxiety management during fertility work-up and ART, current methods can be insufficient in removing all pain and anxiety [1-3]. This thesis explored whether VR, a relatively new and increasingly studied intervention, could improve pain and anxiety management during outpatient benign gynaecological procedures. It was applied during HSG and oocyte retrieval in IVF/ICSI treatment to reduce procedural pain and anxiety. Virtual Reality could accomplish this by immersing patients in a virtual environment, thereby distracting them from the medical procedure [4,5]. The systematic review with meta-analysis in Chapter 2 showed VR contributory in reducing overall pain and procedural anxiety, with limited side effects. This suggests that VR is a safe option for gynaecological patients, which is in line with other studies who applied VR in the pediatric field [6] and burn patients undergoing rehabilitation [7]. Nonetheless, it can be questioned whether VR provides clinically relevant pain reduction. The meta-analysis showed a difference in overall pain scores of 0.98 units (scale 0-10) in favour of VR. Similarly, Eijlers et al. who studied VR in pediatric care found a difference in pain scores of 1.3 units (scale 0-10) in favour of VR [6]. A previous study that aimed to define clinically relevant pain reduction in moderate pain (score 6 in NRS) found that a reduction of 1.3 units in NRS was considered minimal improvement, whereas a reduction of 2.4 units in NRS was considered much improvement [8]. As the results of the meta-analysis corresponded to minimal improvement at most, it can be questioned whether VR provides clinically relevant pain reduction. Furthermore, it is possible that VR is more effective when both pain and anxiety are targeted. An association between pain and anxiety has been proven and a previous study found pre-operative anxiety a predictor of post-operative pain in patients undergoing laparoscopic hysterectomy [9,10]. Therefore, a randomized study on

the effect of VR on pain management during HSG was performed in Chapter 3, and a second randomized study on management of pain and anxiety during oocyte retrieval in IVF/ICSI treatment in Chapter 4.

In Chapter 3 we provided VR during HSG and found no difference in reported overall and worst pain scores between women receiving VR and women not receiving VR. One explanation for this lack of effect on pain was that the sound on the VR application was switched off. This could have resulted in suboptimal immersion in the VR environment, where previous studies found this one of the most contributing factors to successful pain reduction [11,12]. In addition, it is possible that VR is only effective for a subgroup of patients, and not all patients undergoing a certain procedure. This is substantiated by the finding in Chapter 3 where we found higher reported pain scores in women receiving VR compared to the control group, when adjusting for the expectation that VR would provide distraction. Women who have low expectations of VR might therefore experience more benefit during the procedure. Next, it is possible that VR only provides pain reduction to a certain point but is unable to remove all pain when this exceeds a certain level or duration of the procedure. This statement can be substantiated by the fact that all studies who found VR effective in optimizing pain management provided this during gynaecological procedures where pain was considered mild to moderate in severity, e.g. hysteroscopy, IUD insertion and episiotomy repair [13]. Finally, it might be that VR is more effective in reducing procedural anxiety rather than pain, for example during hysteroscopy [14].

Therefore, in Chapter 4 we focused on the effect of VR on anxiety, with pain as a second primary outcome. We found no overall differences in pain and anxiety between women undergoing retrieval with VR and without VR. However, an interaction analysis revealed that when 10 follicles or less were harvested, women receiving VR reported significant lower pain scores than the control group. We did not find this difference in anxiety scores. This might suggest that VR might benefit certain subgroups rather than all patients. Since pain and anxiety are closely linked, adequately reducing (pre-)procedural anxiety might also lead to optimal pain management. Furthermore, VR might also be more effective at reducing anxiety during the waiting period before the procedure. A systematic review on anxiety and pain management during hysteroscopic procedures found that this period was very stressful leading to increased anxiety. Ultimately, anxiety was found the main factor that negatively affected patient experiences [15]. Additionally, previous studies showed that the prevalence of depressive symptoms was twice as high among infertile women. Psychiatric disorders were seen in 40% of the infertile patient population where anxiety disorders were most common followed by a major depressive disorder [16]. Furthermore, Schaller et al. found that IVF/ICSI treatment caused a significant psychological burden on couples but especially on women, leading to premature treatment discontinuation [17]. All this underlines the importance of offering psychosocial support to the infertile couple.

FUTURE PERSPECTIVES IN INFERTILITY

It could be of interest to further study which patients will benefit most from a VR intervention A systematic review on effect modifiers of VR in pain management found that it was most effective among younger patients in moderate to severe pain [18]. This is interesting, as we found VR only effective in retrievals where 10 follicles or less were harvested, which are thought to be quicker and less painful. To the best of our knowledge, there are currently no studies investigating which specific subgroup of patients might benefit most from VR. Furthermore, it can be questioned whether the infertile patient is the right patient group to receive a VR intervention. They already had to change their expectations and experience a loss of control over when and how they become pregnant. They do however have control over how they undergo the oocyte retrieval, and might therefore want to be fully present without their eyes being covered by the VR intervention. In future studies, it could be interesting to include patient preferences by use of interviews and study their views on anxiety and pain management during IVF/ICSI treatment. In addition, both the study described in Chapter 3 and Chapter 4 did not specifically tailor the VR intervention to the patient or the procedure. Not all patients react similarly both to procedural pain, anxiety and to the VR intervention. Furthermore, they might want to gain different things from the VR intervention or need different stimuli in order to achieve optimal anxiety and pain management. Hoffman et al. (2000) was one of the first to ever to study immersive VR, by providing an interactive game called "*Spider world*" to burn patients undergoing physical therapy.

They found that both pain and time spent thinking about pain was reduced [19]. Already at that time, they stated that further research was needed to explore ways of maximizing analgesia effectiveness. Phelan et al. (2023) studied the factors that could improve VR efficacy and found that for burn patients, the VR intervention had to include cartoonish features to optimize positive emotions and interactive features to optimize distraction. Also, the VR intervention had to be used even after the therapeutic session was over, which all optimized the efficacy of the VR intervention [20]. Finally, a pilot study by Pardini et al. found that a personalized VR intervention was more effective in reducing patient reported anxiety and tension, compared to a standard VR intervention. They stated that further research was needed [21]. To the best of our knowledge there are no studies investigating which factors should be added to the VR intervention during outpatient benign gynaecological procedures, to optimize its efficacy. In future studies, it is interesting to add patient perspectives when developing new VR software, for example through interview studies, on their need regarding the outline of the provided VR intervention during a gynaecological procedure, in order to optimize pain and anxiety management.

PART II: STANDARDIZING PAIN MANAGEMENT AND THE APPLIANCE OF SPINAL CORD STIMULATION IN ENDOMETRIOSIS

Although there are recommendations regarding pain management for endometriosis in the ESHRE guidelines [22], currently no clear step-by-step recommendations exist other than the WHO Pain Ladder. However, this was developed for use in oncological patients and might therefore not be suitable for patients experiencing chronic endometriosis symptoms [23]. In Chapter 5, the multidisciplinary consensus meeting followed by a modified eDELPHI procedure aimed to reach national consensus and create a step-by-step guideline for pain management in the endometriosis patient. Through a multidisciplinary consensus meeting with experts from the field of Gynaecology and Obstetrics, Colorectal Surgery, Anesthesiology, Urology and Gastro-Enterology, a flow diagram on pain management for endometriosis patients was created. This was then tested in two rounds of an eDELPHI procedure. Ultimately, this led to a step-by-step guideline. Where the first two steps adhered to the WHO approach [23] and consisted of paracetamol followed by NSAIDs, the third step in endometriosis management entailed the addition of TCAs in case of neuropathic pain. It is recommended to only apply metamizol and opioids short term, for example during the hospitalization period after surgery. Muscarinic receptor antagonists are accepted treatment for bladder endometriosis. Where COX-2 inhibitors can be prescribed as an option, they were not presented as an established step in pain management. A previous study found that up to 19% of women diagnosed with endometriosis experienced no pain relief at all from pharmacological treatment. Moreover, even when treatment provided symptom relief, recurrence of pain symptoms after medical treatment cessation was reported in up to 34% of treated women [24]. Overall, almost one-third of patients who undergo surgery for endometriosis-related pain complaints do not benefit from the treatment, and no predictors of response to surgical treatment have been identified [25]. This underlines the importance of increasing the options regarding endometriosis pain management, especially for endometriosis patients with intractable pain who have already exhausted all treatment options. Here, Spinal Cord Stimulation (SCS) might offer a solution. SCS is a known treatment for neuropathic pain that is reimbursed for certain indication. It has also been found effective in reducing visceral pain [26,27]. Good quality evidence from randomized studies is lacking with most studies being observational in design and of low quality with many retrospective cohorts, case series and case reports. Nonetheless, in Chapter 6 we collected all evidence regarding the effectiveness of neuromodulation on visceral pain – which included SCS, sacral neuromodulation (SNM) and Peripheral Nerve Stimulation (PNS) – caused by multiple conditions including endometriosis. The included studies showed improvement of symptoms, QoL and reduced analgesics use. These results were seen across multiple diagnoses including chronic pancreatitis, bowel and anorectal disorders, urological disorders but also chronic pelvic pain (CPP) because of endometriosis. Furthermore, it seemed that SCS for CPP due

to endometriosis was more effective than for CPP due to other diagnoses [28]. Since these findings were based on low quality studies without a randomized design, we underlined the need for sound, prospective and preferably randomized controlled studies with an adequate number of patients and substantial follow-up.

In Chapter 7 we conducted a feasibility pilot study among nine women suffering from intractable, endometriosis-related pain with a follow up period of 12 months. We found that eight out of nine participants experienced significant symptom improvement, with significant improvements in CPP and several other pain scores. Even more so, all participants who experienced improvements were able to reduce or even discontinue their pain medication. There also was significant improvement in self-reported QoL scores, as well as in all but one core QoL domains of the EHP-30 questionnaire. Side effects were minor, and easily corrected with small revision surgery. Therefore, SCS seems a safe and very effective treatment method for intractable, endometriosis-related visceral pain. Although the specific working mechanism of SCS on visceral pain remains unclear, there are several thought to lie at the basis of its effectiveness that are described in Chapter 7. They include modulation of the spinothalamic tracts and postsynaptic dorsal column pathways, but also by activation of Aß fibers in the dorsal column and release of ɣ-aminobutyric acid, and finally by targeting visceral sympathetic nerves that play a role in visceral pain [27,29-31]. Furthermore, a negative association has been proven between pain cognition and QoL, underlining the importance of pain optimization, for example by applying SCS [32,33]. It is important however, to perform a randomized study to ensure highest quality evidence and extend the follow-up period to at least 24 months. Most importantly because potential complications, device longevity, and sustainability of pain relief can then be monitored over extended periods of time. Not in the least because long-term follow-up data ensures the most optimal chance of getting SCS for visceral pain reimbursed by Dutch health insurance and to be able to implement this treatment in standard practice.

PART III: DIETARY INTERVENTIONS IN THE CHRONIC ENDOMETRIOSIS PATIENT

There is an increasing interest to apply self-management strategies, both among patients and healthcare providers, that can support the effects of standard treatment methods. One of these self-management strategies is a dietary intervention, where frequently applied diets for endometriosis include the Low FODMAP diet, endometriosis diet and glutenfree diet. In Chapter 8 we studied the effect of the endometriosis diet in women diagnosed with endometriosis, and found positive effects on QoL. The endometriosis diet, an avoidance diet created by women diagnosed with endometriosis, involves the avoidance of nutrients which women noticed provoked or aggravated their symptoms. These nutrients include red meat, dairy products, gluten, sugars and nutrients high in

estrogen (e.g.) soy and black beans [34]. While some studies suggest its effectiveness in symptom reduction and QoL improvement, evidence remains limited [35,36]. No guidelines or specific diet composition exist and data regarding the long-term negative effects of the diet are lacking.

Therefore, in Chapter 9 we further studied the effect of dietary interventions, which included the endometriosis diet and the Low FODMAP diet, on endometriosis-related pain and QoL. FODMAPs are non-digestible carbohydrates found in foods like fruits, vegetables, honey, sweeteners and dairy products. This difficult digestion leads to gas production and thereby luminal distention causing symptoms like bloating, flatulence, abdominal pain and constipation [37-39]. With the Low FODMAP diet, foods containing FODMAPs are first avoided for six to ten weeks to calm down the bowel. After symptom relief, high-FODMAP nutrients are gradually reintroduced to identify triggers leading to a personalized diet [38]. Moore et al. found that the Low FODMAP diet was more effective in reducing symptoms in women diagnosed both with endometriosis and IBS, than in women diagnosed with IBS alone [40]. This was substantiated by the study by Armour et al. [41] and the results from our study in Chapter 9. We found a positive effect of both the Low FODMAP diet and endometriosis diet on endometriosis-related pain and QoL. Women reported significant less deep dyspareunia, dysuria, bloating and tiredness but also significant improved scores in six of eleven QoL domains (measured using the EHP-30 questionnaire) when comparing baseline to six month follow-up scores. Nonetheless, since endometriosis is often associated with or even confused with Irritable Bowel Syndrome (IBS) [22], it is possible that the Low FODMAP diet mostly affects IBS-related symptoms, rather than endometriosis-related symptoms. Furthermore, a placebo and Hawthorne effect might have influenced the positive results. Patients knowingly applied a method they thought contributory in symptom reduction and avoided nutrients they thought harmful. This might have resulted in them experiencing symptom and QoL improvement [42,43].

For both diets it is important to realize that some of the avoided nutrients are part of a full-fledged diet and that their implementation can lead to nutritional deficiencies. With the Low FODMAP diet, there is a risk of inadequate intake of carbohydrate and calcium. Gluten are avoided with the endometriosis diet, while regular consumption of whole grain foods (high in gluten) is strongly associated with a significant reduction in diabetes mellitus, cardiovascular disease, intestinal inflammatory disorders, colon cancer risk and better weight management [44-48]. Furthermore, gluten and dairy can support a healthy gut microbiome where their avoidance can lead to dysbiosis and a weakened gut lining. This allows particles like bacteria or digested food to enter the bloodstream, triggering an immune response that can cause inflammation and lead to mild disease. However, when the toxins build up and there is ongoing inflammation this can accumulate into severe disease. Therefore, maintaining a balanced diet is key to preserving gut health and

overall well-being [49]. It is not recommended to apply a diet independently but to do so under supervision of a registered dietician, to ensure properly supplementation of the avoided nutrients and careful monitoring of body weight, particularly during long-term diet adherence. Also because due to its restrictive nature, there is a risk of developing disordered eating habits [44]. Registered dieticians deliver evidence-based therapy, will base the diet on the patients' symptom pattern, have to apply to an ethical code of practice, and ensure that new research data is generated in their field [50-52].

Finally, while a glutenfree diet has been proven effective in treating inflammatory conditions like Crohn's disease and Celiac Disease (CD), a positive impact on endometriosis-related pain has also been suggested but scientific evidence is very limited. Our opinion regarding the appliance of a glutenfree diet, the uncertainties and more so the scientific basis for advising against it can be found in Chapter 10. The suggestion to adhere to a glutenfree diet for endometriosis was solely based on the study by Marziali et al. where data was not corrected for CD and a control group was lacking. This makes it possible that the diet only influenced CD symptoms rather than endometriosis-related symptoms. Additionally, they did not correct for the influence of a nocebo and/or placebo effect. De Graaf et al. underlined the presence of a nocebo effect in gluten intake in their recent study, where the expectancy to eat gluten-rich bread (E+) or not (E-) and actually consuming gluten-rich bread (G+) or not (G-) were used to create and compare four groups [53]. They found that the combination of an expectancy and actually eating gluten-rich bread (E^+G^+) had the largest impact on overall and several individual gastro-intestinal symptoms compared to the other groups [54]. In addition, the Nurses Health' Study II by Schwartz et al. thought it unlikely that gluten intake was a strong factor in endometriosis etiology and symptomatology [52]. Consequently, adopting a glutenfree diet is currently not recommended for alleviating endometriosis-related symptoms.

FUTURE PERSPECTIVES IN ENDOMETRIOSIS CARE

The period between the first onset of endometriosis-related symptoms and the actual diagnosis can be delayed due to the large variety of symptoms, a lack of awareness regarding the diagnosis and an inability to diagnose endometriosis by some healthcare providers. Previously, this resulted in a diagnostic delay in the Netherlands of up to 10.2 years [55]. However, due to the increasing awareness of endometriosis in recent years, but also improvements in diagnostic methods, this has led to a shortened diagnostic delay of 7.4 years [55]. The report by the Dutch Society of Obstetrics and Gynaecology (NVOG) on the impact of female-specific conditions, saw that the number of registered diagnoses of endometriosis in the Dutch healthcare system increased from 14.248 in 2019 to 17.007 in 2022 [56]. Therefore, the group of diagnosed endometriosis patients in the Netherlands with need for symptom management has become larger in recent years.

In addition, there is a growing reluctance among women to use hormones and oral contraceptives (OCs). They are 'pill tired' and feel that OCs do not align with a healthy lifestyle because they supposedly have a negative effect on the nutrient status, may affect their mood or disrupt their natural hormonal balance. A recent study found that among sexually active girls under 25 years of age, the use of oral contraceptives dropped from 76% in 2012 to 46% in 2023, with 1 in 5 girls not using any contraceptives at all [57]. These changes were not seen in figures from the Dutch Central Bureau of Statistics (CBS) of the general female population aged 16 to 49, which might suggest that 'pill tiredness' is a trend primarily among younger women which is most likely induced and/or maintained through non-medical influencers on social media [58]. However, experience from general practice and reading of internet blogs learns that reluctance to use hormones is common across all age groups. This has contributed to an increasing interest in non-hormonal alternatives for endometriosis-related symptoms like Spinal Cord Stimulation (SCS) or self-management strategies. It is crucial to research these alternatives, to provide healthcare providers with evidence-based guidance for patients. Finally, endometriosis has a large societal impact that is comparable to Diabetes Mellitus Type II for example [59]. In 2022, the total healthcare costs related to endometriosis were €19.200.140,- with total societal costs per patient of approximately €9579,- [56,59]. By optimizing endometriosis management, these costs could be reduced. All this underlines the importance of broadening treatment options for visceral, endometriosis-related pain.

Part II found SCS for intractable visceral endometriosis-related pain a very effective treatment method. There are some mechanisms thought to lie at the basis of its effectiveness but none have been confirmed in scientific studies. This makes that investigation of the precise mechanisms by which SCS alleviates visceral pain is considered important. By understanding the involved neural pathways and neurotransmitter interactions, the effectiveness of SCS could be enhanced and lead to more targeted therapies where it is tailored to the patient. This in turn ensures that SCS is effective for as much patients as possible. Another contributing factor can be to perform subgroup analyses, aiming to refine patient selection criteria. By identifying which patients are most likely to benefit from SCS for visceral pain this can improve treatment outcomes, reduce unnecessary interventions and thereby lower healthcare costs. There also is a positive environmental element due to less medical waste from unnecessary treatment. By optimizing stimulation parameters such as pulse width, frequency, and amplitude, SCS settings can be personalized to optimize its effect on visceral pain, while minimizing side effects at the same time. Currently, high associated costs (approximately €21.000,-- per patient in the first 12 months) have led to SCS being applied as last resort treatment. However, there was large cost saving on medical costs but also on the patient and their family and productivity gained for society due to the large efficacy of SCS. This led to an estimated cost saving of €800,-- per patient/year in favour of SCS, making it cost-effective in 80% of cases [60]. Therefore, there is an increasing call amongst healthcare providers to apply SCS sooner

in the sequence of pain management options, and not as last resort after all hormonal, pain management and surgical options have been exhausted. The positive effects of our feasibility study regarding the effect of SCS on symptoms and QoL could substantiate this statement. Also because the high costs of SCS are compensated by long-term improvements in symptoms and health-related QoL [61,62]. This underlines the importance of performing a cost-analysis analysis (CEA), also because it can simplify getting reimbursement by the Dutch Healthcare Institute for the indication "*visceral pain related to endometriosis*".

In Part III another solution in managing intractable, endometriosis-related pain was described: a dietary intervention. There are indications that this could be effective in reducing endometriosis-related pain. However, it can be questioned whether these effects are fully attributed to the dietary intervention, or whether there is a large psychosocial component associated with it. To our knowledge however, there are no specific studies on this subject. A previous study performed at the Amsterdam UMC provided the ENDOCARE questionnaire to women receiving endometriosis care in Dutch secondary and tertiary centers, which is able to identify factors women consider important in their healthcare and healthcare providers. They stated that 'Emotional support and alleviation of fear and anxiety' needed the most improvement [63]. A strong relationship with a healthcare provider is crucial, as patients tend to feel a greater sense of control and relief when it is positive, whereas dissatisfaction with care often leads to patients seeking alternatives. Moreover, the ability to take an active role in disease management and effective collaboration with the healthcare provider is positively associated with satisfaction of care [64].

Finally for all research, not just research in our group of infertile and endometriosis patients, it is important to look at pain with the biopsychosocial model in mind. This model does not only look at the linear relationship between the extensiveness of the disease and the experienced symptoms, but also takes physical, psychological and social factors into account and their effect on one another [65]. When treating a disease, it is therefore important to also include patient preferences, expectations and experiences rather than just symptom management and study the impact of pain management strategies on health domains they consider relevant. This way, the effect of SCS and dietary interventions is studied from a holistic approach which can include its effect on pain, but also on QoL, pain-related depression and anxiety or fatigue. The importance of studying efficacy of treatment from a more holistic approach is not only underlined by patients, but also by healthcare providers [66]. Studying the effect can be done by establishing Minimal Clinically Important Change Scores (MCID) which represent the minimal level of clinical improvements the patient considers beneficial in their situation. There are certain limitations to these MCIDs such as recall bias and impossibility to generalize their results due to patient population variability but can assist in assessing patient improvement across all areas of treatment [67]. This helps to prevent situations where patients report lower pain scores, leading healthcare providers to view the treatment as effective, while the patient remains

bedridden and unable to engage in daily activities or participate in society. In conclusion, we underline the importance of studying interventions from a holistic approach in future studies.

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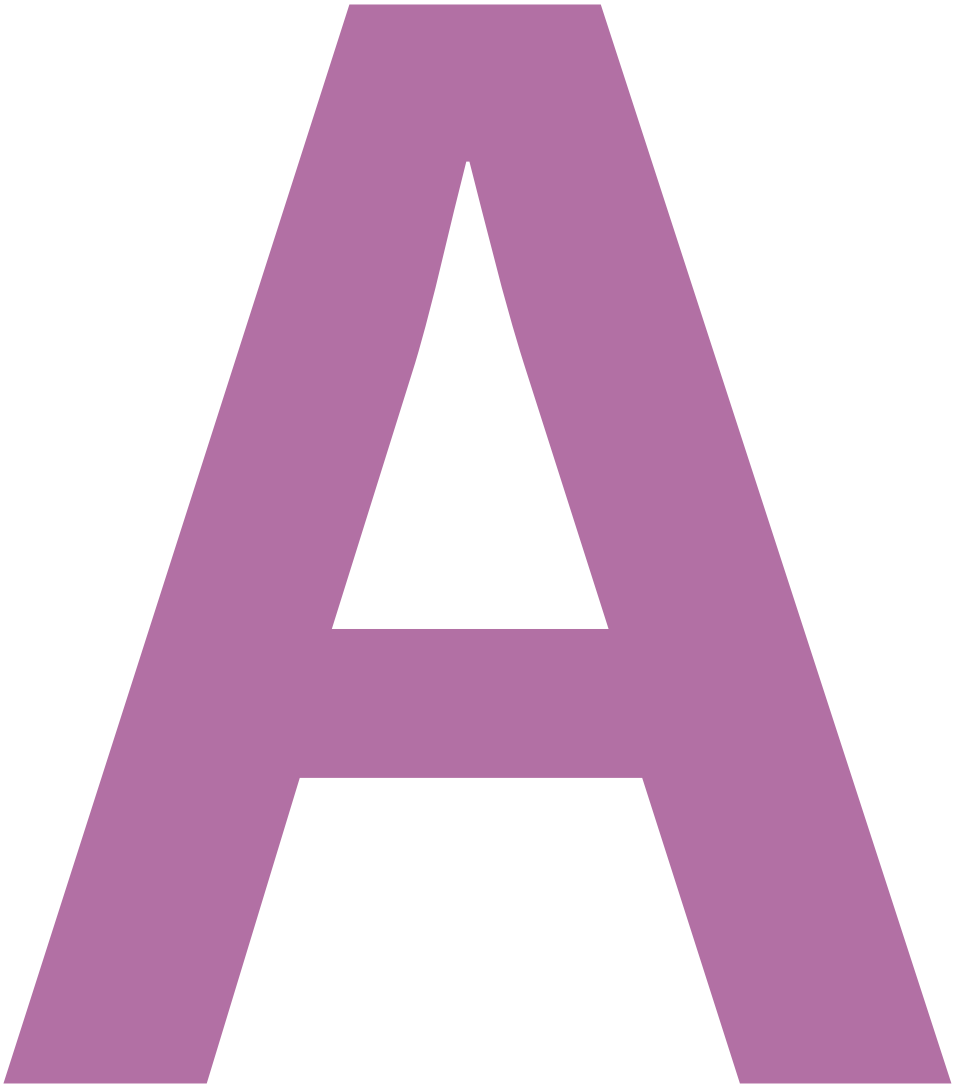

Appendices

English Summary
Nederlandse Samenvatting
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ENGLISH SUMMARY

This thesis centers around alleviating pain and anxiety, and thereby optimizing patient experiences, in the infertile and endometriosis patient. We focused on innovative approaches like Virtual Reality (VR) and Spinal Cord Stimulation (SCS), but also self-management strategies including dietary interventions which are emerging among endometriosis patients worldwide. The results are presented in three parts: **Part I** focused on pain and anxiety management in infertile women by using Virtual Reality. **Part II** focused on developing a step-by-step approach in pain management for endometriosis by using an eDELPHI procedure, and the appliance of SCS in women suffering from intractable visceral pain caused by endometriosis. Finally, **Part III** focused on the effect of different dietary interventions on pain and quality of life (QoL) among women diagnosed with endometriosis. Box 1 summarizes all research questions with the answers as presented in this thesis. Finally, the discussion reflects on the results and puts forward new perspectives for the future.

Part I: Pain and anxiety management using Virtual Reality in the infertile patient

In previous studies VR has been found effective in reducing both pain and anxiety during (acute) medical procedures. By reducing pain and anxiety, patient experiences and satisfaction can also be improved. In **Chapter 2** all evidence regarding the appliance of VR in (outpatient) gynaecological procedures was collected, and a meta-analysis was performed. A reduction in worst pain and procedural anxiety during gynaecological procedures was seen, in favour of VR. In addition, four studies reported on satisfaction scores. All satisfaction scores were high with no significant difference in patient satisfaction between VR and non-VR. Improved satisfaction scores are considered important, since they are associated with better treatment outcomes, enhanced therapy compliance, less healthcare provider visits, diminished malpractice litigation and an improved prognosis. In **Chapter 3** we studied the effect of VR on pain during hysterosalpingography (HSG). We found no disparity in reported average and worst pain scores between women receiving VR and women not receiving VR. When pain scores were corrected for the expectation that VR would be a good distraction from pain during HSG, we found that women reported significant higher overall and worst pain scores. Failure to meet the expectation that VR provides distraction and thus pain reduction, may play a role in this. Nonetheless, women undergoing HSG with VR expressed significantly less willingness to undergo another HSG without VR, compared to women undergoing HSG without VR. It can therefore be concluded that there was high patient satisfaction.

Similarly, in **Chapter 4** we evaluated the efficacy of VR on pain and anxiety management during oocyte retrieval in IVF/ICSI treatment. We found no significant differences in anxiety, overall pain and peak pain between participants receiving VR and participants not

receiving VR. When looking at retrievals where 10 follicles or less were collected, we did see a significant benefit of VR on overall pain. It might be that VR is only effective up to a certain pain threshold or duration of the procedure. Where pain experienced during oocyte retrieval is manageable at first with the use of VR, it might become insufficient after a while when the pain intensifies and the duration of the procedure takes longer. The use of standard VR interventions might explain the lack of effect in this study. Not all patients react similarly and they might want to gain similar things from the VR intervention in order to achieve optimal anxiety and pain management. It can also be questioned whether infertile patients undergoing IVF/ICSI treatment are the right people to provide VR software to. They already had to change their expectations and experience a loss of control over when and how they become pregnant, but do have control over how they undergo oocyte retrieval.

Box 1. Answers to the research questions of this thesis

Part I

Q1. What is the effect of Virtual Reality (VR) on pain, anxiety and patient satisfaction during (outpatient) gynaecological procedures?

A1. VR can reduce worst pain scores and pre-procedural anxiety. This can improve patient experiences and satisfaction. This is important since it is associated with better treatment outcomes, enhanced therapy compliance, reduced healthcare provider visits, diminished malpractice litigation and an improved prognosis.

Q2. Does Virtual Reality (VR) contribute to pain relief during fertility work-up?

A2. Virtual Reality does not contribute to pain relief when applied during HSG. However, patients undergoing an HSG with VR were significantly less willing to undergo an HSG without VR again, compared to women who underwent an HSG without VR. Therefore, we consider patient satisfaction with VR during HSG to be high.

Q3. Does Virtual Reality (VR) contribute to pain and anxiety relief during oocyte retrieval in IVF/ICSI treatment?

A3. Virtual Reality does not contribute to pain relief when applied during IVF/ICSI treatment. VR was effective in retrievals with 10 follicles or less, suggesting it might be effective in shorter procedures.

Part II: Standardizing pain management and the appliance of Spinal Cord Stimulation in endometriosis

Until recently, there was no step-by-step approach to pain management in endometriosis treatment. Therefore, in **Chapter 5** we performed a multidisciplinary consensus meeting followed by an eDELPHI procedure to reach national consensus and a step-by-step guideline for pain management in endometriosis patients. Where the first two steps adhere to

the WHO step-by-step approach and consist of paracetamol followed by NSAIDs, the third step in our flow diagram consisted of the addition of Tricyclic Antidepressants (TCAs) in case of neuropathic pain. Both the use of metamizol, part of the NSAID group but causing agranulocytosis in long-term use, and opioids with a highly addictive character, are recommended to only be used short-term, for example during hospitalization after surgery. Muscarinic receptor antagonists are accepted treatment for bladder endometriosis. The use of COX-2 inhibitors were suggested but not presented as an established step in pain management as scientific evidence in human studies is lacking. It was advised to prescribe magnesium oxide with all types of pain management because of their positive effect on gastro-intestinal symptoms. Finally, proton pump inhibitors (PPIs) should be prescribed with use of NSAIDs, also when incidental.

In **Chapter 6** we collected all evidence regarding the appliance of SCS for visceral pain, between a broad number of diagnoses. We concluded that SCS applied for visceral pain could be effective in reducing symptoms, improving QoL and in reducing of even discontinuing pain medication use. However, complication rates, particularly with older devices, call for caution when applying SCS. Nonetheless, it seems effective and we found that SCS was more effective for patients diagnosed with endometriosis compared to other diagnoses. We considered it important that sound, prospective and preferably randomized controlled studies, with an adequate sample size and substantial follow-up are conducted in the future. Therefore, in **Chapter 7** we performed a feasibility pilot study, where SCS was applied specifically in women diagnosed with endometriosis and intractable pain. We found that SCS was effective in reducing general and worst pain, dysmenorrhea, chronic pelvic pain, dysuria and dyschezia when comparing baseline to different follow-up moments. The follow-up period entailed 12 months. We saw improvements both in the self-reported QoL scores and in all but one of the core domains of the EHP-30 questionnaire. All participants but one were able to reduce their analgesics. Unfortunately, one participant requested device explantation due to lack of effect at 12 month follow-up.

Box 1. Continued

Part II

Q1. What would be considered standard pain management in endometriosis patients?

A1. The first two steps consist of paracetamol followed by NSAIDs. As a third step, TCAs could be applied. COX-2 inhibitors are presented as an option. Opioids and metamizol should only be prescribed short term. Muscarinic receptor antagonists are an accepted treatment for bladder endometriosis.

Q2. Could Spinal Cord Stimulation be an effective treatment for visceral pain?

A2. SCS could be an effective treatment for visceral pain caused by a wide range of diagnoses. It can reduce symptoms, improve QoL and reduce or even discon-

tinue pain medication use. Since there are high complication rates, certain caution should be implied when applying SCS.
Q3. What is the effect of Spinal Cord Stimulation on pain and QoL in women diagnosed with endometriosis, experiencing intractable visceral pain?
A3. SCS is effective in reducing general and worst pain, endometriosis-related symptoms such as dysmenorrhea and chronic pelvic pain. It is effective in improving QoL scores and all but one core domains of the EHP-30 questionnaire. Users might also be able to reduce their pain medication.

Part III: Dietary interventions in the chronic endometriosis patients

Because standard treatment can be insufficient in reducing endometriosis-related symptoms or may be accompanied with unacceptable side effects there is an increasing interest in self-management strategies among healthcare providers and patients. One of these self-management strategies is a dietary intervention. In **Chapter 8** we performed a survey study on the effect of the endometriosis diet on quality of life. We found that the endometriosis diet positively influenced QoL, even more so when there was strict adherence. We underlined the importance of identifying facilitators and barriers to dietary adjustments in women diagnosed with endometriosis. Therefore, we conducted a pilot study in **Chapter 9** on the efficacy of the endometriosis diet and Low FODMAP diet on pain and QoL. We also included potential facilitators to improve dietary adherence. We found that a diet positively influenced pain scores in deep dyspareunia, dysuria, bloating en tiredness and improved QoL in six out of eleven EHP-30 domains (used to measure QoL in women diagnosed with endometriosis) after six months. We found no influence of self-reported strictness scores on the effectiveness of the dietary intervention. Over time, women reported that dietary adherence became more easy, and applying it in their daily life became easier. In addition, we provided them with materials to optimally adhere to their chosen diet. Not only the endometriosis diet and Low FODMAP diet, but also a glutenfree diet has frequently been mentioned to be effective in reducing endometriosis-related symptoms.

While a glutenfree diet can be effective in treating celiac disease, scientific evidence supporting the claim that it could also be effective in treating endometriosis-related symptoms is limited. In **Chapter 10** we discussed why a glutenfree diet should not be recommended to women solely diagnosed with endometriosis. Its efficacy is based on only one study by Marziali et al. without a control group. In addition, no participants were testing for coeliac disease. Therefore it is possible that a strong placebo and nocebo effect, and not an actual effect, plays a crucial role in the effectiveness of a glutenfree diet in endometriosis. Women noticed symptom relief when they avoided a nutrient they thought was harmful for them. Nonetheless, there is no actual effect of a glutenfree diet on endometriosis-related symptoms. Therefore, women diagnosed with endometriosis

should be recommended to adhere to healthy dietary guidelines, as advised by the World Health Organization (WHO). This obviously does not apply if there is an additional diagnosis of coeliac disease (CD).

Box 1. Continued

Part III

Q1. What is the effect of a Low FODMAP diet and endometriosis diet on pain and quality of life in women diagnosed with endometriosis?

A1. The Low FODMAP diet and endometriosis diet can have a positive effect on pain and QoL in women diagnosed with endometriosis. It is debatable whether strictness scores influence the effect of dietary interventions.

Q2. Can a glutenfree diet be recommended to women diagnosed with endometriosis, and is there sufficient scientific evidence to do so?

A2. There is insufficient scientific evidence to substantiate the recommendation of adherence to a glutenfree diet in patients diagnosed with endometriosis. Instead, women diagnosed with endometriosis should be recommended to adhere to healthy dietary guidelines as advised by the WHO. An exception of course, is when there is an additional diagnosis of celiac disease.

NEDERLANDSE SAMENVATTING

In dit proefschrift staat het optimaliseren van pijn en stress management centraal, zowel bij infertiele patiënten als bij patiënten gediagnosticeerd met endometriose. Door dit te optimaliseren, werd eveneens gepoogd om patiëntervaringen te optimaliseren. In dit proefschrift werden innovatieve methoden zoals Virtual Reality (VR) en Spinal Cord Stimulation (SCS) onderzocht, alsook zelfmanagement strategieën zoals dieetinterventies welke wereldwijd steeds meer populariteit verkrijgen onder endometriose patiënten. De resultaten van dit proefschrift worden gepresenteerd in drie delen: **Deel I** onderzocht pijn en stress management in infertiele vrouwen door middel van Virtual Reality. In **Deel II** werd een stappenplan in het pijnmanagement bij endometriose ontwikkeld middels een eDELPHI procedure. Daarnaast werd gekeken naar het toepassen van SCS in vrouwen met onbehandelbare viscerale pijn, onder andere veroorzaakt door endometriose. **Deel III** keek naar het effect van dieetinterventies op pijn en kwaliteit van leven in vrouwen gediagnosticeerd met endometriose. Box 1 vat alle onderzoeksvragen samen, met daaronder de gevonden antwoorden in de verschillende onderzoeken van dit proefschrift. Ten slotte reflecteert de discussie op alle gevonden resultaten, worden nieuwe perspectieven voor de toekomst naar voren gebracht en worden aanbevelingen gedaan voor toekomstig onderzoek.

Deel I: Pijn en stress management middels Virtual Reality bij infertiele vrouwen

In eerdere studies is al gezien dat VR effectief kan zijn in het verminderen van pijn en stress tijdens (acute) medische procedures. Door het verminderen van pijn en stress kunnen ook de ervaringen en tevredenheid van de patiënten verbeterd worden. In **Hoofdstuk 2** werden alle onderzoeken over het gebruik van VR in gynaecologische behandelingen verzameld, en werd een meta-analyse uitgevoerd. Een vermindering in ergste pijnscores en pre-procedurele stress werd gezien tijdens gynaecologische behandelingen wanneer VR werd toegepast. Daarnaast rapporteerden vier van de zes studies over de patiënt tevredenheid. Deze waren allen hoog, echter werd geen significant verschil lieten gezien in tevredenheidsscores tussen VR en geen VR. Het verbeteren van patient tevredenheid wordt als belangrijk gezien, omdat dit geassocieerd wordt met betere behandeluitkomsten, verbeterde therapietrouw, minder bezoek aan zorgverleners, minder rechtszaken wegens wanpraktijken en een betere prognose. In **Hoofdstuk 3** werd het effect van VR op pijn tijdens hysterosalpingografie (HSG) onderzocht. Hier werd geen verschil gezien in de gemiddelde en ergste pijnscore, tussen vrouwen die tijdens het HSG wel VR of geen VR interventie ontvingen. Wanneer we corrigeerden voor de verwachting dat VR een goede afleiding zou zijn tijdens het HSG, ontdekten we dat zelfs significant hogere pijnscores werden gerapporteerd. De verwachting dat VR voor afleiding en daarmee pijn vermindering zorgt, iets wat vervolgens niet waargemaakt wordt, kan hierin een rol spelen. Wel waren vrouwen die een HSG met VR ondergingen aanzienlijk minder bereid om

nogmaals een HSG zonder VR te ondergaan. Hieruit kan geconcludeerd worden dat er sprake was van hoge patiënt tevredenheid.

In **Hoofdstuk 4** onderzochten we het effect van VR op pijn en stress tijdens een eicelpunctie, wat onderdeel is van een IVF/ICSI behandeling. We vonden geen verschillen zowel in angst als in gemiddelde en ergste pijnscore tussen deelnemers zonder danwel met een VR interventie tijdens de eicelpunctie. Wanneer gekeken werd naar puncties waarbij 10 follikels of minder werden verzameld, werd wel een significant positief effect gezien van VR op de gemiddelde pijnscore. Dit kan mogelijk verklaard worden door het feit dat VR alleen effectief is tot een bepaalde pijngrens of duur van de procedure. Wanneer de ervaren pijn in eerste instantie beheersbaar is dankzij VR, kan deze na verloop van tijd onvoldoende worden wanneer de pijn intenser wordt en/of de procedure langer duurt. Het gebruik van VR interventies die niet op maat gemaakt zijn voor de patiënten kan het gebrek aan effect in deze studie verklaren. Niet alle patiënten reageren op dezelfde manier en willen mogelijk op andere manieren afgeleid worden, om op die manier optimale angst- en pijnbeheersing te verkrijgen. Het is ook de vraag of patiënten die een IVF/ICSI-behandeling ondergaan de juiste personen zijn om VR-software te verschaffen. Ze moesten hun verwachtingen al bijstellen en hebben geen controle meer over wanneer en hoe ze zwanger worden, maar hebben wel controle over hoe ze de eicelpunctie ondergaan.

Box 1. Antwoorden op de onderzoeksvragen in dit proefschrift

Deel I

Q1. Wat is het effect van Virtual Reality (VR) op pijn, stress en patiënt tevredenheid tijdens poliklinische gynaecologische behandelingen?

A1. VR kan ergste pijnscores en pre-procedurele stress verminderen. Dit kan patient ervaringen en patient tevredenheid verbeteren. Dit is belangrijk, omdat het geassocieerd is met betere behandelingsuitkomsten, verbeterde therapietrouw, minder bezoek aan zorgverleners, minder rechtszaken wegens wanpraktijken en een betere prognose.

Q2. Draagt Virtual Reality (VR) bij aan pijnvermindering tijdens oriënterend vruchtbaarheidsonderzoek?

A2. VR draagt niet bij aan pijnvermindering, wanneer het aangeboden wordt tijdens het HSG. De verwachting dat VR voor afleiding zou zorgen, heet een negatieve invloed op pijnscores. Wel waren vrouwen die het HSG ondergingen met VR significant minder bereid om het HSG opnieuw te ondergaan zonder VR, vergeleken met vrouwen die het HSG zonder VR ondergingen. Daarom denken wij in dat patiënt tevredenheid tijdens het HSG, wanneer VR toegepast wordt, hoog is.

Q3. Draagt Virtual Reality (VR) bij aan pijn en stressvermindering tijdens een eicelpunctie, uitgevoerd in het kader van een IVF/ICSI behandeling?

A3. Virtual Reality draagt niet bij aan pijnvermindering wanneer het wordt toegepast tijdens de punctie in het kader van een IVF/ICSI behandeling. VR was effectief bij tijdens puncties van 10 follikels of minder. Dit suggereert dat het effectief zou kunnen zijn bij kortere procedures.

Deel II: Optimaliseren van pijn management en de toepassing van Spinal Cord Stimulation voor endometriose

Tot voorkort was er geen stappenplan ten aanzien van pijnmanagement bij endometriose. Daarom werd in **Hoofdstuk 5** een multidisciplinaire expert meeting georganiseerd, gevolgd door twee digitale DELPHI rondes. Zo werd gepoogd om consensus onder Nederlandse endometriose experts te bereiken, over een stappenplan voor pijn management bij endometriose patiënten. Waar de eerste twee stappen hetzelfde waren als de WHO pijnladder en bestonden uit paracetamol gevolgd door NSAIDs, bestond de derde stap in ons flow diagram uit tricyclische antidepressiva (TCA's) wanneer er sprake was van neuropathische pijn. Het wordt aanbevolen om zowel het gebruik van metamizol, welke tot de NSAID-groep behoort maar bij langdurig gebruik agranulocytose kan veroorzaken, als het gebruik van opioïden met een sterk verslavend karakter, zo kort mogelijk te houden, bijvoorbeeld tijdens ziekenhuisopname na een operatie. Muscarine receptor antagonisten zijn een geaccepteerde behandeling wanneer er sprake is van endometriose laesies op de blaas. Het gebruik van COX-2 remmers werd beschreven als optie maar niet als een vaststaande stap in pijnbestrijding. Dit omdat wetenschappelijk bewijs beperkt is en met name bestaat uit dierstudies. Er werd geadviseerd om magnesiumoxide voor te schrijven bij alle soorten pijnbestrijding vanwege het positieve effect op gastro-intestinale symptomen. Ten slotte werd geadviseerd om protonpomp-remmers (PPI's) voor te schrijven bij gebruik van NSAIDs, ook wanneer dit gebruik incidenteel is.

In **Hoofdstuk 6** werden alle studies verzameld waarin SCS toegepast werd voor viscerale pijn. Hierin werd een breed scala aan diagnoses meegenomen, die ten grondslag kunnen liggen aan viscerale pijn. Wij concludeerden dat SCS succesvol toegepast kan worden voor viscerale pijn omdat het kan zorgen zowel voor symptoomvermindering, alsook voor een verbetering van de kwaliteit van leven en de mogelijkheid om pijnmedicatie af te bouwen of zelfs helemaal te staken. Onder vrouwen met viscerale pijn veroorzaakt door endometriose, lijkt SCS zelfs effectiever. Echter, gezien de complicaties die kunnen voorkomen bij SCS, met name onder de oudere SCS systemen, is voorzichtigheid geboden. Het uitvoeren van grote, gerandomiseerde studies in de toekomst, met een adequaat aantal proefpersonen en een lange follow-up duur, is van cruciaal belang. Daarom voerden wij in **Hoofdstuk 7** een pilotstudie uit, waarbij gekeken werd naar de haalbaarheid van het toepassen van SCS. Het werd toegepast bij vrouwen gediagnosticeerd met endometriose die kampten met therapie-resistente, endometriose-gerelateerde klachten. Wij vonden dat SCS effectief was in het verminderen van de algemene en meest

ernstige pijnscores, maar ook endometriose-gerelateerde symptomen zoals dysmenorroe, chronische bekkenpijn, dysurie en dyschezia. Bovendien zagen we verbeteringen in zowel de zelf gerapporteerde kwaliteit van leven scores als in alle kerndomeinen van de EHP-30-vragenlijst, op één na. Acht van de negen deelnemers konden hun pijnstillers verminderen. Helaas vroeg een deelnemer om verwijdering van het SCS systeem na 12 maanden, vanwege een gebrek aan effect.

Box 1. Vervolg

Deel II

Q1. Wat wordt gezien als standaard behandeling bij vrouwen gediagnosticeerd met endometriose?

A1. De eerste twee stappen bestaan uit paracetamol gevolgd door NSAID's. Als derde stap kunnen TCA's worden toegepast. COX-2-remmers worden als optie gepresenteerd. Opioïden en metamizol mogen alleen voor korte termijn worden voorgeschreven. Muscarine receptorantagonisten zijn een geaccepteerde behandeling voor endometrioselaesies op de blaas.

Q2. *Is spinal cord stimulation (SCS) een effectieve behandeling voor viscerale pijn?*

A2. SCS kan een effectieve behandeling zijn voor viscerale pijn, binnen een breed scala aan diagnoses die viscerale pijn veroorzaken. SCS kan bijdragen aan het verminderen van symptomen en het verbeteren van QoL verbeteren. Ook kan het bijdragen aan de mogelijkheid om pijn medicatie af te bouwen of zelfs geheel staken. Omdat er een groot aantal complicaties kan voorkomen bij SCS, is voorzichtigheid geboden bij het toepassen ervan.

Q3. Wat is het effect van spinal cord stimulation (SCS) op pain en QoL, onder vrouwen gediagnosticeerd met endometriose en therapie-resistente, viscerale pijn?

A3. SCS is effectief in het verminderen van algemene en hevige pijnscores, maar ook endometriose-gerelateerde symptomen zoals dysmenorroe en chronische bekkenpijn. Het is effectief in het verbeteren van kwaliteit van leven scores en alle kernonderdelen van de EHP-30-vragenlijst, op één na. Gebruikers kunnen mogelijk ook hun pijnmedicatie verminderen.

Deel III : Dieet interventies bij chronische endometriose patiënten

Er is niet altijd voldoende effect van de standaardbehandeling op het verminderen van alle endometriose-gerelateerde symptomen. Daarnaast kan het gepaard gaan met onacceptabele bijwerkingen. Daarom is er toenemende interesse in het toepassen van zelfmanagement strategieën, zowel onder zorgverleners als onder patiënten. Een van deze zelfmanagement strategieën is een dieetinterventie. In **Hoofdstuk 8** voerden wij een vragenlijstonderzoek uit, waarbij gekeken werd naar het effect van het endometriosedieet op de kwaliteit van leven. Wij vonden dat het endometriosedieet een positieve invloed

had op de kwaliteit van leven, waarbij personen die zich strikt aan het dieet hielden dit zelfs nog meer ervoeren. Ook werd het belang onderstreept van het identificeren van factoren die dieetadhesie vergemakkelijken, en barrières die het bemoeilijken. Daarom werd in **Hoofdstuk 9** een pilot studie uitgevoerd, waarbij gekeken werd naar de effectiviteit van het endometriosedieet en het Low FODMAP dieet op pijn en kwaliteit van leven. Er werden ook factoren meegenomen die dieetadhesie mogelijk vergemakkelijkten. Wij vonden een positieve invloed van het dieet zowel op endometriose-gerelateerde klachten als op de kwaliteit van leven. Na zes maanden dieetadhesie ervoeren vrouwen minder diepe dyspareunie, dysurie, een opgeblazen gevoel en vermoeidheid. Daarnaast rapporteerden ze een betere score in zes van de elf EHP-30 domeinen, welke gebruikt wordt om de kwaliteit van leven van endometriose patiënten te meten. Er werd geen verschil gezien wanneer vrouwen zich strikt aan het dieet hielden. Na verloop van tijd ervoeren vrouwen dat het volgen van een dieet gemakkelijker werd, en dat het beter in te passen was in hun dagelijks leven. Daarnaast werden participanten voorzien van materialen om het door hen gekozen dieet zo optimaal mogelijk te volgen.

Niet alleen het endometriosedieet en het Low FODMAP-dieet maar ook een glutenvrij dieet wordt vaak genoemd als effectieve methode voor het verminderen van endometriose-gerelateerde klachten. Een glutenvrij dieet is bewezen effectief in de behandeling voor coeliakie maar het wetenschappelijk bewijs ten aanzien van endometriose is zeer beperkt. In **Hoofdstuk 10** bespraken we waarom een glutenvrij dieet niet aanbevolen zou moeten worden aan vrouwen alléén gediagnosticeerd met endometriose. De effectiviteit ervan is gebaseerd op slechts een onderzoek van Marziali et al., waarbij geen gebruik gemaakt werd van een controlegroep. Bovendien werd geen enkele deelnemer getest op de aanwezigheid van coeliakie. Daarom is het mogelijk dat een sterk placebo- en nocebo-effect, en niet een daadwerkelijk effect, een cruciale rol speelt in de effectiviteit van een glutenvrij dieet bij vrouwen gediagnosticeerd met endometriose. Vrouwen merken verbetering van klachten wanneer zij een voedingsmiddel vermijden waarvan zij geloven dat het slecht voor ze is. Er is echter geen daadwerkelijk effect aangetoond van een glutenvrij dieet op endometriose-gerelateerde klachten. Daarom zou vrouwen gediagnosticeerd met endometriose moeten worden aanbevolen om zich te houden aan de eetrichtlijnen voor gezonde voeding, zoals opgesteld door de Wereldgezondheidsorganisatie (WHO). Dit geldt uiteraard niet als er sprake is van coeliakie (CD).

Box 1. Vervolg

Deel III

Q1. Wat is het effect van het Low FODMAP dieet en endometriosedieet op pijn en kwaliteit van leven (QoL) onder vrouwen gediagnosticeerd met endometriose?

A1. Het Low FODMAP dieet en endometriosedieet hebben een positief effect op pijn en kwaliteit van leven, onder vrouwen gediagnosticeerd met endometriose. Het is de vraag of strikte adhesie aan een dieet het effect van voedingsinterventies kan beïnvloeden.

Q2. *Kan een glutenvrij dieet aangeraden worden aan vrouwen gediagnosticeerd met endometriose, en is er voldoende wetenschappelijk bewijs om dit te doen?*

A2. Er is onvoldoende wetenschappelijk bewijs om een glutenvrij dieet aan te raden aan vrouwen gediagnosticeerd met endometriose. Daarom zou geadviseerd moeten worden om zich aan de eetrichtlijnen voor gezonde voeding te houden, zoals opgesteld door de Wereldgezondheidsorganisatie (WHO). Dit geld uiteraard niet wanneer er eveneens een diagnose van coeliakie is.

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† Attributing to PhD thesis

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LIST OF AUTHORS

Co-autors presented in this thesis and their affiliations

Matthanja Bieze
Department of Anesthesia and Pain Management, Erasmus UMC, Rotterdam, the Netherlands

Marlies Bongers
Department of Obstetrics and Gynecology, Máxima Medical Center, Veldhoven, the Netherlands
Grow-School of Oncology and Reproduction, Maastricht University, Maastricht, Netherlands

Fred Brouns
Department of Human Biology, School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands

Bianca De Bie
Endometriose Stichting, Dutch Endometriosis Patient Organization, Sittard, the Netherlands

Judith Dekker
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Kim Dreyer
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Department of Reproductive Medicine, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Misha Erwteman
Department of Anesthesiology and Pain Management, Amsterdam UMC, Amsterdam, the Netherlands

Kris Ferguson
Department of Anesthesiology and Pain Management, Aspirus Langlade Hospital, Pain Clinic, Antigo, Wisconsin, United States of America

David Heineman
Department of Cardiothoracic Surgery, Amsterdam UMC, Amsterdam, the Netherlands

Markus Hollmann
Department of Anesthesiology and Pain Management, Amsterdam UMC, Amsterdam, the Netherlands

Eric van der Horst
Department of Pediatric Urology, Amsterdam UMC, Emma Children Hospital, Amsterdam, the Netherlands

Roos van den IJssel
Department of Urgent Care, Rode Kruis Ziekenhuis, Beverwijk, the Netherlands

Jan Willem Kallewaard
Department of Anesthesiology and Pain Management, Amsterdam UMC, Amsterdam, the Netherlands
Department of Anesthesiology and Pain Management, Rijnstate Ziekenhuis, Arnhem, the Netherlands

Leonardo Kapural
Department of Anesthesiology and Pain Management, Carolina's Pain Institute and Center for Clinical Research, Winston Salem, North Carolina, United States of America

Disha Karim
Department of Gynaecology and Obstetrics, University of Gent, Ghent, Belgium
Department of Gynaecology and Obstetrics, Erasmus UMC, Rotterdam, the Netherlands

Daniël Keszthelyi
Department of Internal Medicine, Gastroenterology-Hepatology, Maastricht University Medical Center+, Maastricht, the Netherlands
Department of Human Biology, *School for Nutrition and Translational Research in Metabolism,* Maastricht University, Maastricht, the Netherlands

Esther Kuijper
Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Haarlem, the Netherlands

Cornelis Lambalk
Department of Reproductive Medicine, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Robert de Leeuw
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Sean Li
Department of Anesthesiology and Pain Management, National Spine and Pain Centers, Shrewsbury, New Jersey, United States of America

Jacques Maas
Department of Gynaecology and Obstetrics, Maastricht UMC+, Maastricht, the Netherlands
Grow-School of Oncology and Reproduction, Maastricht University, Maastricht, the Netherlands

Ingeborg Melgers
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Velja Mijatovic
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Endometriosis Center, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Ben Willem Mol
Department of Gynaecology and Obstetrics, Monash University, Clayton, Australia
Department of Gynaecology and Obstetrics, Aberdeen Centre for Women's Health Research, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom

Annemiek Nap
Department of Gynaecology and Obstetrics, Radboud UMC, Nijmegen, The Netherlands

Jakko Nieuwenhuijzen
Department of Urology, Amsterdam UMC, Amsterdam, the Netherlands
Cancer Center Amsterdam, Imaging and Biomarkers & Cancer Treatment and Quality of Life, Amsterdam, the Netherlands

Michael Schatman
Department of Anesthesiology and Pain Management, Perioperative Care & Pain Medicine, NYU Grossman School of Medicine, New York, United States of America
Department of Population Health, Division of Medical Ethics, NYU Grossman School of Medicine, New York, United States of America

Merel Oskam
Department of Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands

Anneke Schreurs
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Endometriosis Center, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Nino Tonch
Department of Reproductive Medicine, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Jurriaan Tuynman
Department of Surgery, Colorectal Surgery, Amsterdam UMC, Amsterdam, the Netherlands
Endometriosis Center, Amsterdam UMC, Amsterdam, the Netherlands

Kristien Tytgat
Department of Gastro-Enterology, Amsterdam UMC, Amsterdam, the Netherlands

Kimmy Rosielle
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Koen Venema
Centre for Healthy Eating & Food Innovation (HEFI), Maastricht University, Maastricht, the Netherlands

Stijn Vlek
Department of Surgery, Colorectal Surgery, Amsterdam UMC, Amsterdam, the Netherlands
Endometriosis Center, Amsterdam UMC, Amsterdam, the Netherlands

Aileen de Vogel
Dietician Practice Aileen de Vogel, Dordrecht, The Netherlands

Ralph de Vries
Medical Library, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

Madelon van Wely
Department of Gynaecology and Obstetrics, Amsterdam UMC, Amsterdam, the Netherlands
Amsterdam Reproduction and Development Research Institute, Amsterdam, the Netherlands

Jane Wijbers
Endometriosis Center, Amsterdam UMC, Academic Medical Center, Amsterdam, the Netherlands

AUTHOR CONTRIBUTIONS

Chapter 2 – Reducing pain and anxiety with Virtual Reality in Gynaecological procedures: a systematic review with meta-analysis.

Annelotte van Haaps, Merel Oskam, Kim Dreyer, Kimmy Rosielle, Ralph de Vries, Ben Willem Mol, Madelon van Wely, Jan Willem Kallewaard, Anneke Schreurs, Velja Mijatovic.

Study design and concept: Annelotte van Haaps, Merel Oskam, Kim Dreyer, Velja Mijatovic. Literary search: Ralph de Vries. Data analysis and interpretation: Annelotte van Haaps, Merel Oskam. Writing manuscript – original draft: Annelotte van Haaps. Manuscript editing and review: all authors.

Conflict of interest: Annelotte van Haaps: travel support from Merck. Kim Dreyer: travel and speakers fees, research grants from Guerbet and Ferring. Kimmy Rosielle: travel support from Merck. Ben Willem Mol: Research funding from NHMRC and Merck, consultancy and travel fees from Merck, Organon, and Norgine. Stock folder for ObsEva. Madelon van Wely: co-editor for Cochrane Gynaecology and Fertility. Jan Willem Kallewaard: Consulting fees and member of advisory board of Boston Scientific, Saluda, Nevro, Abbott, Medtronic. Board member of BNS. Anneke Schreurs: travel grant from ESHRE as invited speaker. Velja Mijatovic: travel and speakers fees, research grants from Guerbet and Ferring.

Chapter 3 - No pain relief by Virtual Reality during hysterosalpingography (HSG): results from a randomized controlled trial

Kimmy Rosielle, Annelotte van Haaps, Esther Kuijper, Nino Tonch, Disha Karim, Merel Oskam, Roos van den IJssel, Ben Willem Mol, Nils Lambalk, Kim Dreyer, Velja Mijatovic.

Study design and concept: Kimmy Rosielle, Annelotte van Haaps, Nils Lambalk, Kim Dreyer, Velja Mijatovic. Data collection: Kimmy Rosielle, Annelotte van Haaps, Disha Karim, Merel Oskam, Roos van den IJssel. Data analysis and interpretation: Kimmy Rosielle, Annelotte van Haaps. Writing manuscript – original draft: Kimmy Rosielle, Annelotte van Haaps. Manuscript editing and review: all authors.

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Chapter 4 - No anxiety and pain reduction by Virtual Reality during oocyte retrieval in IVF/ICSI treatment: results of a randomised controlled trial

Annelotte van Haaps, Anneke Schreurs, Kimmy Rosielle, Velja Mijatovic, Jan Willem Kallewaard, Kim Dreyer.

Study design and concept: Annelotte van Haaps, Kim Dreyer, Velja Mijatovic. Data collection: Annelotte van Haaps. Data analysis and interpretation: Annelotte van Haaps. Writing manuscript – original draft: Annelotte van Haaps. Manuscript editing and review: all authors.

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Chapter 5 - Standardizing pain management for the endometriosis patient: a Dutch modified Delphi procedure

Annelotte van Haaps, Anneke Schreurs, Robert de Leeuw, Misha Erwteman, Judith Dekker, Ingeborg Melgers, Eric van der Horst, Jakko Nieuwenhuijzen, Kristien Tytgat, David Heineman, Kim Dreyer, Jan Willem Kallewaard, Velja Mijatovic.

Study design and concept: Annelotte van Haaps, Anneke Schreurs, Robert de Leeuw, Kim Dreyer, Velja Mijatovic. Consensus meeting leader: Anneke Schreurs. Consensus meeting participants: Misha Erwteman, Judith Dekker, Ingeborg Melgers, Eric van der Horst, Jakko Nieuwenhuijzen, Kristien Tytgat, David Heineman, Kim Dreyer, Velja Mijatovic. eDELPHI design: Robert de Leeuw. eDELPHI distribution: Jan Willem Kallewaard, Velja Mijatovic.

Data analysis and interpretation: Annelotte van Haaps, Robert de Leeuw, Anneke Schreurs, Kim Dreyer, Velja Mijatovic. Writing manuscript – original draft: Annelotte van Haaps. Manuscript editing and review: all authors.

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board of Boston Scientific, Saluda, Nevro, Abbott, Medtronic. Board member of BNS. Velja Mijatovic: travel and speakers fees, research grants from Guerbet and Ferring.

Chapter 6 - Spinal Cord Stimulation for Intractable Visceral Pain Originating from the Pelvic and Abdominal Region: A Narrative Review on a Possible New Indication for Patients with Therapy-Resistant Pain.

Matthanja Bieze, Annelotte van Haaps, Leo Kapural, Sean Li, Kris Ferguson, Ralph de Vries, Michael Schatman, Velja Mijatovic, Jan Willem Kallewaard.

Study design and concept: Matthanja Bieze, Jan Willem Kallewaard. Literature search: Matthanja Bieze, Ralph de Vries. Data collection: Matthanja Bieze, Annelotte van Haaps. Data analysis and interpretation: Matthanja Bieze, Jan Willem Kallewaard, Annelotte van Haaps. Writing manuscript – original draft: Matthanja Bieze. Manuscript editing and review: all authors.

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Chapter 7 - Spinal Cord Stimulation for intractable, visceral pain associated with endometriosis: results on a feasibility study.

Annelotte van Haaps, Jan Willem Kallewaard, Matthanja Bieze, Misha Erwteman, Annemiek Nap, Markus Hollmann, Anneke Schreurs, Velja Mijatovic.

Study design and concept: Jan Willem Kallewaard, Misha Erwteman, Annelotte van Haaps, Velja Mijatovic. Patient recruitment: Annelotte van Haaps, Jan Willem Kallewaard, Velja

Mijatovic. Data collection: Annelotte van Haaps, Jan Willem Kallewaard, Jack Dunselman, Esther Franx, Dorien Rodestein, Elizabeth Nanne. Data analysis and interpretation: Annelotte van Haaps. Writing manuscript – original draft: Annelotte van Haaps. Manuscript editing and review: all authors.

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Chapter 8 - A better quality of life could be achieved by applying the endometriosis diet: a cross-sectional study in Dutch endometriosis patients.

Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Velja Mijatovic.

Study design and concept: Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Velja Mijatovic. Participant recruitment and data collection: Jane Wijbers. Data analysis: Annelotte van Haaps. Interpretation of data: Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Velja Mijatovic. Writing manuscript – original draft: Annelotte van Haaps. Manuscript editing and review: all authors.

Conflict of interest: Velja Mijatovic: travel and speakers fees, research grants from Guerbet and Ferring.

Chapter 9 - The effect of dietary interventions on pain and quality of life in women diagnosed with endometriosis: a prospective study with control group.

Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Stijn Vlek, Jurriaan Tuynman, Bianca De Bie, Aileen de Vogel, Madelon van Wely, Velja Mijatovic.

Study design and concept: Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Stijn Vlek, Jurriaan Tuynman, Velja Mijatovic. Participant recruitment and data collection: Jane Wijbers, Annelotte van Haaps. Dietary guidance: Jane Wijbers. Supervision dietary guidance: Aileen de Vogel. Data analysis: Madelon van Wely, Annelotte van Haaps. Interpretation of data: Annelotte van Haaps, Jane Wijbers, Anneke Schreurs, Velja Mijatovic. Writing manuscript – original draft: Annelotte van Haaps. Manuscript editing and review: all authors.

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dometriosis patients outside the study. Speakers fees for educational lectures from Albert Schweitzer hospital. Madelon van Wely: co-editor for Cochrane Gynaecology and Fertility. Velja Mijatovic: travel and speakers fees, research grants from Guerbet and Ferring.

Chapter 10 - Diet associations in endometriosis: a critical narrative assessment with special reference to gluten.

Fred Brouns, Annelotte van Haaps, Daniël Keszthelyi, Koen Venema, Marlies Bongers, Jacques Maas, Velja Mijatovic.

Study design and concept: Fred Brouns. Data collection: Fred Brouns. Written parts belonging to their expertise: Annelotte van Haaps, Velja Mijatovic, Jacques Maas, Daniël Keszthelyi, Koen Venema**.** Writing manuscript – original draft: Fred Brouns. Manuscript editing and review: all authors.

PHD PORTFOLIO

Courses

- 2024 Biostatistics Amsterdam UMC Doctoral School 1.4 ECTs
- 2023 Research Integrity course Amsterdam UMC Doctoral School 2 ECTs
- 2023 Scientific Writing in English Amsterdam UMC Doctoral School 3 ECTs
- 2020 eBROK course The Netherlands Federation of University Medical Centers 1.5 ECTs

International and national presentations

- 2025 Boston Scientific Pain Academy. Keynote speaker on *Spinal Cord Stimulation for visceral pain: a new indication for patients with therapy-resistant pain.* Madrid, Spain.
- 2025 4th European Congress of the International Neuromodulation Society (INS). Oral Poster Presentation, poster and ePoster presentation on *Spinal Cord Stimulation for visceral pain: a new indication for patients with therapy-resistant pain?*. Istanbul, Turkey.
- 2024 16th World Congress of the International Neuromodulation Society (INS). Oral Poster Presentation, Poster and ePoster presentation on *Spinal Cord Stimulation for visceral pain: a new indication for patients with therapy-resistant pain?* Vancouver, Canada.
- 2024 Research dag Anesthesiologie, Amsterdam UMC. Oral presentation on *Spinal Cord Stimulation for visceral pain: a new indication for patients with therapy-resistant pain*.
- 2023 World Congress Endometriosis (WCE). Three Poster Presentations. (1) *Spinal Cord Stimulation for intractable visceral and neuropathic pain related to endometriosis : a two-center prospective feasibility study.* (2) *A better quality of life could be achieved by applying the endometriosis diet : a cross sectional study in Dutch endometriosis patients.* (3) *The effect of Dietary Interventions on Pain and Quality of life in women diagnosed with endometriosis : a prospective study with control group*. Edinburgh, United Kingdom.
- 2023 39th Annual Meeting of the European Society of Human Reproduction (ESHRE). Poster Presentation on *The effect of Dietary Interventions on Pain and Quality of life in women diagnosed with endometriosis: a prospective study with control group.* Copenhagen, Denmark.
- 2023 3rd European Congress of the International Neuromodulation Society (eINS). Poster Presentation on *Spinal Cord Stimulation for intractable visceral and neuropathic pain related to endometriosis : a two center prospective feasibility study.* Hamburg, Germany.
- 2023 FC Noord Holland. Oral presentation on *Virtual Reality in Gynaecological Care.*
- 2021 Wetenschapsdag Anesthesiologie. Oral presentation on *Spinal Cord Stimulation for intractable chronic lower abdominal neuropathic pain caused by endometriosis.*

Nominations and Awarded grants

- 2023 Part of the "biggest papers of the year" from RBM-Online, which garnered the most attention. A better quality of life could be achieved by applying the endometriosis diet: a cross-sectional study in Dutch endometriosis patients.
- 2023 Eggcelent Change grant by Theramex for Virtual Reality for anxiety and pain management during oocyte retrieval in IVF/ICSI treatment (VitRo study). €5.000,--.
- 2021 Co-author of grant ZonMw Implementation- and scale-up coaching (round four) for Virtual Reality as anxiety and pain management during oocyte retrieval in IVF/ICSI treatment (VitRo trial). €5.000,--.

Teaching

- 2024 Salma Asrih Alami. Bachelor thesis. Neuromodulation for endometriosis-related pain: a novel development in pain management.
- 2022 Ana Curiel. Bachelor thesis. The influence of dietary or nutritional intervention on endometriosis-related (pain) symptoms: a systematic review.
- 2022 Janine van den Hoorn. Master thesis. Endometriosis Diet and experienced Quality of Life in Social and Societal participation.
- 2022 Roos van den IJssel. Master thesis. Virtual Reality for Pain Relief in Hysterosalpingography: a randomized controlled trial.
- 2021 Merel Oskam. Master thesis. Virtual Reality for pain relief in hysterosalpingography.

Extra-curricular activities

- 2024 Member of organization committee Amsterdam Reproduction and Development Retreat 24 – 25 October. Theme: Ar&Dificial Intelligence
- 2023 – 2024 Treasurer of Obstetrics and Gynaecology Researchers association (OVGO – Onderzoekersvereniging Obstetrie en Gynaecologie)
- 2023 Member of organization committee Amsterdam Reproduction and Development Retreat 2 – 3 November. Theme: All AboA&rD!

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Lieve Saartje, we startte samen in Delft, zaten dagelijks in dezelfde trein en woonden toevallig bij elkaar om de hoek. Onze treinreis naar huis was altijd een moment om even bij te komen van een drukke dag, alle situaties nog even de revue te laten passeren, alle frustratie eruit de gooien en te roddelen over van alles en nog wat. Het jaar dat wij samen heen en weer reisden naar Delft was voor mij alles behalve een makkelijk jaar, dankjewel dat ik bij jou voor alles terecht kon. Fijn dat we elkaar, ook nu onze wegen gescheiden zijn, blijven spreken.

Allerliefst S.P.H.I.N.X. jaar '12. Toen ik als guppie van 18 aankwam in Amsterdam, één groot tranendal omdat ik eigenlijk niet goed wist waar ik me voor had aangemeld, had ik nooit durven dromen dat ik vriendinnen voor het leven zou vinden. *Lieve Mattie*, ik ben zo blij dat jij je niet door 'feut deco' liet afschrikken. *Lieve KJ*, ik bewonder jouw doorzettingsvermogen en niemand verdient dat plekje bij de derma meer dan jij. *Lieve Bingie*, jij luistert écht, onthoud alles en kan er na maanden nog op terugkomen. Dankjewel voor jouw lieve, oprechte interesse. *Lieve Coesie*, jouw ambitie en hoe hard jij werkt, vind ik enorm inspirerend. Ik probeer daarin vaker te zijn als jij. En natuurlijk worden je outfits regelmatig gekopieerd. *Lieve Moos,* veel mensen zullen situaties zien welke verbetering behoeven, dat erkennen maar het daar bij laten. Jij daarentegen gaat over tot actie en doet er daadwerkelijk iets aan. *Lieve Guus*, jij vecht als een leeuwin voor je dierbaren, maar bent ook niet bang om voor je mening uit te komen. Ik ben zo blij dat jij het geluk bij Pien hebt gevonden. *Lieve Frankie*, the hostess met the mostest, degene die ervoor zorgde dat wij elkaar bleven zien, we missen je nu zo ver weg in Thailand. Ik bewonder hoe jij altijd een positieve draai weet te geven aan de tegenslagen in het leven. *Lieve Pippa,* jij hebt mij geleerd dat misschien niet alles meteen hoeft. Ik hou van onze gesprekken over manifesteren, die mij laten inzien dat ik niet altijd met twee benen op de grond hoeft te staan. *Lieve Suuzie,* degene die ons verrast met aankondigingen over nieuwe vriendjes en baby's op komst. Onze sportochtenden met koffie nadien op zondag zijn me enorm dierbaar. Dankjewel dat jij me altijd aanmoedigt, zonder eigen mening luistert en adviezen geeft. En me die extra push geeft wanneer het nodig is. *Lieve Mees,* het meisje wat ik wachtend in de rij voor de Kleine Cooldown tegenkwam, en meteen in mijn hart heb gesloten. Jij werkt hard, praat bijna net zo hard en hebt een sociaal leven waar ik altijd

een beetje jaloers op ben. Zoveel vrienden van alle verschillende clubjes en sporten om je heen verzameld, voor wie je allemaal tijd weet te maken. Jij gaat voor je vriend(inn)en door het vuur en steunt ze onvoorwaardelijk. Dankjewel dat je ook op deze dag naast me staat. *Lieve SPHINX '12 jaarbaby's*, jullie hebben allemaal een speciaal plekje in mijn hart en ik hoop dat er nog velen bij mogen komen.

Liefste oudste vriendinnen van het BC. Lieve bitchessss (ja, met 4x S). Ooit las ik ergens dat, wanneer je langer dan 10 jaar bevriend bent, dit vriendschappen voor het leven zijn. Ik geniet ervan dat we, ondanks dat we allemaal verschillende paden bewandeld hebben, elkaar altijd weer terug vinden tijdens onze borrelavonden en dinertjes.

Dan voelt het altijd weer even alsof we tieners zijn op de mozaïekbank van de aula. Onze vriendschap heeft een vanzelfsprekendheid, waarin we elkaar volledig accepteren. Dank jullie wel voor onze 20 jaar vriendschap en liefde.

Lieve familie van der Mee. Lieve Do, Fem, Wiebe, Bente, Ties, Wisse, Annika, Irsa en Isaak. Dank dat jullie mij direct in jullie midden opgenomen hebben en voor alle warmte en gezelligheid die ik van jullie gekregen heb. *Lieve Walter*, hopelijk kijk jij mee van boven. Je was een geweldig lieve schoonvader. Als familiemens had jij het heerlijk gevonden dat iedereen voor deze gelegenheid weer een excuus had om bij elkaar te komen.

Lieve Ard, Luck en Quinten, mijn drie bonusbroers. Het kan niet altijd makkelijk voor jullie geweest zijn om ineens met zoveel vrouwen deel uit te maken van een gezin. Dat je flauwe grappen met een side eye ontvangen worden. Ik vind het bijzonder dat het zo makkelijk gevoeld heeft om met z'n allen deel uit te maken van dit samengesteld gezin. Jullie drie hebben mij altijd een heel welkom gevoel gegeven. Ik ben jullie enorm dankbaar daarvoor. *Lieve An, Anna, Kim* en *Mees*. Jullie zijn de leukste schoonzussen en -broer die iemand zich kan wensen. *Lieve Wandertje*, jij bent een heerlijk ventje, een knuffelkont en een acteur in de dop. Misschien inspireert dit boekje je om later, als je niet de private equity ingaat, je oom en tante achterna te gaan met een PhD.

Lieve Gert, dank dat jij mijn moeder zo gelukkig maakt, dat jij drie extra kinderen in je hart gesloten hebt en ons direct het gevoel gegeven hebt dat wij onderdeel zijn van jouw gezin. Dank voor alle steun, alle gesprekken en voor alle wijze raad; ook al luister ik niet altijd naar je. Dank dat jij voor mij een vaderrol hebt willen invullen, waar die met mijn eigen vader zo vreselijk ingewikkeld is.

Lieve mamma, jij bent mijn allergrootste voorbeeld. Dankjewel voor het warme, liefdevolle nest waarin wij drieën hebben mogen opgroeien. Volgens mij hebben we het altijd heel goed gehad met z'n vieren. Voor het gevoel van onvoorwaardelijke liefde maar ook het duwtje in de rug en streng toespreken wanneer ik soms iets te veel bezig was met

biertjes drinken op de sociëteit. Jij hebt altijd het beste voor ons gewild en ik heb altijd de oneindige trots van jou gevoeld wanneer we het goed doen.

Lieve oma, ik voel me gezegend dat jij nog steeds bij me bent, en dat je vandaag aanwezig kan zijn bij dit bijzondere moment. Ik koester onze band en de tripjes samen van Friesland tot Roermond, al is het voor jou ook al goed om samen te eten in Den Haag. Bij jou voel ik me altijd welkom, en kunnen we het samen over alles hebben. Dankjewel voor alle steun en liefde die ik te allen tijde van jou krijg.

Lieve Thijs, mijn grote kleine broertje. Waar we er vroeger niet anders in hadden kunnen staan, ik ijverig huiswerk makend op zolder en mee joelend op de muziek en jij juist veel relaxter, zijn onze paden toch akelig op elkaar gaan lijken. Jij alleen vele malen sportiever dan ik. Ik kijk vol verwondering naar hoe jij werkt, sport als een professional en ook nog tijd vind om vluchtelingen Nederlands te leren. Ik ben je dankbaar dat jij zo achter je zussen staat. De band die wij hebben met z'n drieën is me oneindig dierbaar.

Lieve Lara, mijn kleine zusje die allang zo klein niet meer is maar toch altijd 12 blijft in de ogen van haar broer en zus. Waar ik vroeger misschien gedacht heb dat ik een aankleedpop kreeg, heb jij nooit interesse gehad voor al dat prinsessengedoe. Ik heb bewondering voor jouw standvastigheid, dat je weet wat je waard bent en daar ook voor op je strepen blijft staan. Je bent een enorme doorzetter en ik ben blij dat jij je draai gevonden hebt met allemaal lieve mensen om je heen. Al ben je net zo eigenwijs als ik, en botst dat af en toe, wij weten precies wat we aan elkaar hebben en kunnen we voor alles bij elkaar terecht.

Lieve Beer, jij hebt het mij vorig jaar niet makkelijk gemaakt, maar ik kwam er ook achter dat ik het leven simpelweg niet zonder jou wilde doen. Dankjewel dat je sinds mijn start in de kliniek zo voor mij gezorgd hebt. Mij alle ruimte hebt gegeven om me volledig op mijn carrière te concentreren en mijn draai daar te vinden. Dat je zo'n cheerleader voor me bent en me overweldigd met complimenten. Door jouw ogen voel ik me de slimste en mooiste vrouw op aarde. Met je vrolijkheid maak jij het leven lichter. Daarnaast is jouw enthousiasme over je eigen werk aanstekelijk, wat maakt dat ik mijn werk ook net weer dat beetje extra leuk ga vinden. Al wordt het na 10 jaar toch eindelijk tijd voor die ring.

OVER DE AUTEUR



Annelotte van Haaps werd op 27 april 1994 geboren in 's Gravenhage. Zij woonde daar de eerste twee jaar van haar leven, waarna ze met haar ouders, Marlies en Jan Pieter, en jongere broer Thijs verhuisde naar Heemstede. Daar werd haar jongste zusje Lara geboren. Op haar 7de verhuisden ze naar Gorssel waar Annelotte opgroeide. Haar ouders zijn op haar 9e uit elkaar gegaan. Beide ouders hebben inmiddels nieuwe partners. Zij volgde basisonderwijs op de Joppeschool en ging vervolgens naar het Gymnasium van het Baudartius collega te Zutphen. In haar eerste levensjaar moest Annelotte een grote operatie ondergaan voor craniosynostose, waarmee haar interesse in de geneeskunde was gewekt. Toen het in 2012 tijd werd om een studiekeuze te maken schreef zij zich dan ook in voor de studie Geneeskunde aan de Universiteit van Utrecht. Omdat zij werd uitgeloot besloot zij om Biomedische Wetenschappen te studeren aan de Vrije Universiteit van Amsterdam. Daarnaast werd zij lid van het Amsterdamsch Studenten Corps. In 2013 probeerde zij het opnieuw, en werd zij ingeloot voor de studie Geneeskunde aan de Vrije Universiteit van Amsterdam.

Annelottes interesse voor de Gynaecologie werd gewekt in haar wachttijd tussen de Bachelor en Master van de studie Geneeskunde. Zij besloot naar Tanzania af te reizen en als vrijwilliger te werken in het Mount Meru Ziekenhuis te Arusha, op de Obstetrie afdeling. Hier kreeg zij te maken met de geneeskunde op zijn meest primitieve manier, en maakte zij voor het eerst een bevalling mee. Tijdens haar co-schappen in het Amsterdam UMC, locatie VUMC, werd haar liefde voor de Gynaecologie en Obstetrie nog verder bevestigd. Zij besloot daarom haar semi-arts stage in dit vakgebied te doen in het Amstelland ziekenhuis te Amstelveen. Annelotte haalde haar diploma niet lang na de uitbraak van de COVID pandemie in de zomer van 2020. In de eerste maanden van de pandemie werkte Annelotte als zorgondersteuner op de COVID afdelingen van het Spaarne Gasthuis en in de teststraat van GGD Amsterdam. In oktober 2020 begon Annelotte als Protocollendokter bij de afdeling Voortplantingsgeneeskunde van het VU Medisch Centrum. Zij coördineerde meerdere studies welke geïnitieerd werden vanuit andere centra dan het VUMC waaronder de SOMA studie, MYPP studie, Diagnostic Delay Endometriosis studie en de GAS studie. Daarnaast coördineerde zij de multicenter COPIE trial, geïnitieerd vanuit het VUMC. In 2021 startte zij simultaan een promotieonderzoek binnen de Endometriosezorg onder begeleiding van Prof. Dr. Velja Mijatovic, Dr. Jan Willem Kallewaard en Dr. Anneke Schreurs. Dit promotieonderzoek is een samenwerking tussen de Anesthesie en Gynaecologie. Tijdens haar promotietraject had Annelotte meerdere presentaties op internationale congressen en Nederlandse Wetenschapsdagen voor zowel de Anesthesie als Gynaecologie en was zij keynote speaker voor de Boston Scientific Pain Academy te

Madrid. Zij organiseerde twee keer het AR&D Retreat, was actief binnen de Onderzoekersvereniging van het Amsterdam UMC en was gedurende 1 jaar de penningmeester.

In 2024 heeft Annelotte een jaar lang gewerkt als ANIOS Gynaecologie en Obstetrie in het Reinier de Graaf ziekenhuis te Delft. Tegelijkertijd heeft zij haar promotieonderzoek afgerond. Inmiddels heeft zij de overstap gemaakt naar het Onze Lieve Vrouwe Gasthuis te Amsterdam, waar zij eveneens werkt als ANIOS. Annelotte woont samen met haar vriend Berend in Amsterdam.

