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Review

Endometriosis: Etiology, pathobiology, and therapeutic prospects

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SUMMARY

Endometriosis is a common condition associated with infertility that causes chronic pain in many, but not all, women. It is defined by the presence of endometrial-like tissue outside the uterus. Although the cause and natural history of the disorder remain uncertain, hormonal, neurological, and immunological factors are all implicated in the mechanisms contributing to development of symptoms. Because definitive diagnosis requires surgery, there is often a long diagnostic delay after onset of symptoms. Current interventions for endometriosis have limited efficacy and unacceptable side effects/risks and are associated with high rates of symptom recurrence. Here, we review recent advances in our understanding of the etiology of endometriosis, discuss current diagnostic and treatment strategies, highlight current clinical trials, and consider how recent results offer new avenues for the identification of endometriosis biomarkers and the development of effective non-surgical therapies that are fertility-sparing.

INTRODUCTION

Endometriosis is a chronic, neuro-inflammatory condition associated with debilitating chronic pelvic pain estimated to affect 6%–10% of women of reproductive age (Zondervan et al., 2020) (Figure 1). Diagnosis of endometriosis is only considered definitive when the presence of endometrial-like tissue (“lesions”) outside the uterus is confirmed during surgery. Endometriosis lesions can be found in asymptomatic women and are detected in up to 50% of women seeking treatment for infertility (Meuleman et al., 2009). Epidemiological studies report that women with endometriosis lesions are at higher risk of developing ovarian and breast cancer, melanoma, asthma, rheumatoid arthritis, and cardiovascular disease (Kvaskoff et al., 2015).

The diagnosis of endometriosis is often delayed because symptoms, such as pelvic pain and/or infertility (Figure 1), are also associated with other conditions (Horne and Saunders, 2019; Zondervan et al., 2020). Although diagnosis of some types of endometriosis can be accelerated by use of imaging techniques (see below), to date, progress toward validation of a robust non-invasive blood test has been slow (Rižner, 2014). Current treatments include surgical removal of lesions and drugs that suppress ovarian hormone production. Of women undergoing surgery, over half will have a further surgical procedure by 5 years (Saraswat et al., 2018), and many medical treatments have unwanted side effects. Surveys of patients consistently highlight symptom relief and improved medical therapies that do not limit fertility as a top priority for research (Horne et al., 2017; Rogers et al., 2017).

In this review, we summarize recent advances in our understanding of the pathobiology of endometriosis that have been informed by an improved understanding of inflammatory, hormonal, metabolic, and pain pathways. To aid in interpretation of the strengths and weaknesses of the new advances, we provide an overview of the types of endometriosis, current usual practice in diagnosis, and standard surgical and medical treatments. In the final sections, we summarize some of the current clinical trials and consider how recent results offer new avenues for the development of effective non-surgical therapies that are fertility-sparing. In this review, we use the terms "woman" and "women," but it is important to note that endometriosis can affect all assigned female at birth (not only those who identify as women).

ENDOMETRIOSIS: SUBTYPES, SYMPTOMS, AND CLASSIFICATION AS A “DISEASE”

Types of endometriosis and their diagnosis

The majority of diagnosed cases of endometriosis can be broadly characterized into three pelvic cavity subtypes: superficial peritoneal that accounts for ~80% of endometriosis, ovarian (cysts or “endometrioma”), and deep (Horne and Saunders, 2019; Zondervan et al., 2020). Endometriosis lesions have also been found in extra-pelvic sites, including the upper abdominal visceral organs, abdominal wall, diaphragm and pleura (“thoracic endometriosis”), and the central and peripheral nervous system (Andres et al., 2020).

The definitive method to diagnose and stage endometriosis is visualization at surgery (typically involving laparoscopy). In a recent review of the literature, we identified 22 different endometriosis staging systems. The most commonly applied is the revised scoring system of the American Society for Reproductive Medicine (ASRM), used to determine the stage (ranging from I–IV, indicating “minimal” to “severe” endometriosis) on the basis

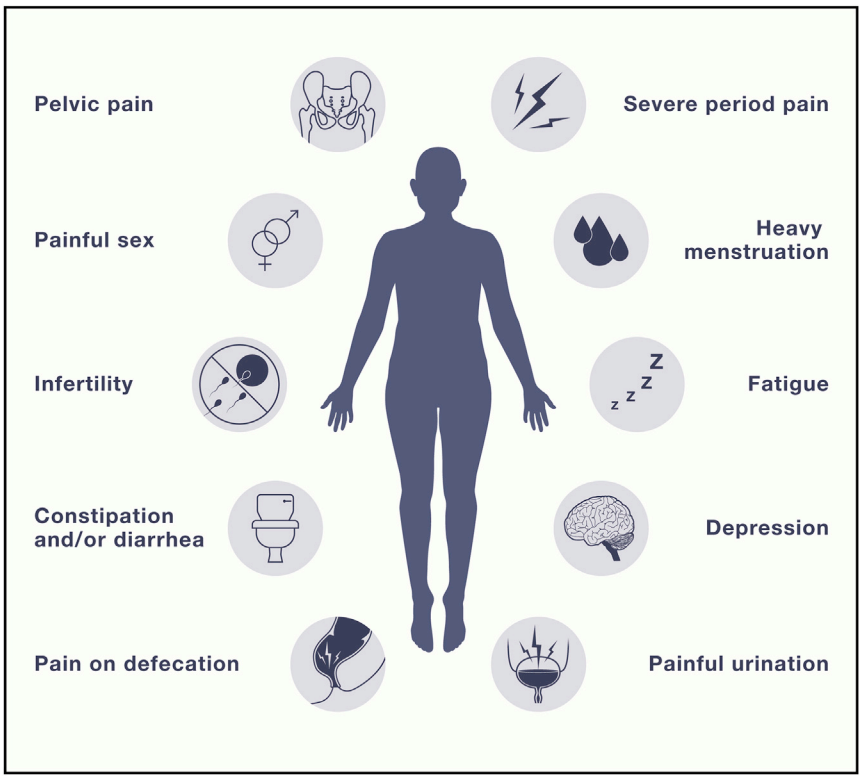

Figure 1. Endometriosis is associated with a wide range of symptoms

Summary of the most common symptoms associated with the condition, including pain, bowel, and bladder symptoms, as well as those that are also associated with other chronic pain conditions, such as fatigue and depression. The ranges of symptoms (that may or may not occur in all patients) contribute to the recognized delay in diagnosis because they overlap with these other conditions.

of the type, location, appearance, and depth of invasion of the lesions, and the extent of disease and adhesions (American Society for Reproductive Medicine, 1997). Non-surgical diagnostic approaches including transvaginal ultrasonography and magnetic resonance imaging (MRI) can be useful in the detection of ovarian and deep endometriosis (Horne and Saunders, 2019).

Symptoms and reclassification as a "syndrome"

Endometriosis is often associated with symptoms such as chronic pelvic pain (cyclical and non-cyclical), painful periods, painful sex, and pain on defecation and urination (Figure 1). In common with other chronic pain conditions, women with endometriosis report suffering from fatigue and depression. Sub/infertility is significantly higher in patients with endometriosis compared to the general female population. Comparisons to disease stage, according to the ASRM criteria, consistently record poor correlations between abundance/location and type of lesions and patient reported pain symptoms (Vercellini et al., 2007). The natural history of the disease is poorly understood with no consensus on whether superficial peritoneal endometriosis can progress to become another subtype or regress spontaneously. The etiology of extra-pelvic endometriosis is even more uncertain.

These uncertainties have led to the suggestion that we may make more progress in developing patient-focused treatments if we stop considering endometriosis as a single "disease" with a diagnosis based solely on the presence of lesion(s) resembling endometrium. We, and others, think the disease model is problematic, not only because of the poor correlation between numbers/location of lesions and pain symptoms, but also because it is estimated that up to 50% of asymptomatic fertile women presenting for other surgical procedures may have lesions. Therefore, we agree with the proposal that endometriosis might be better considered a "syndrome," diagnosed only when a patient has both visible lesions and symptoms, with a greater emphasis being placed on the evaluation of new therapies in a framework that focuses on treating the symptoms most important to the patient as these may vary across the life-course (Hickey et al., 2020).

Developments in the field of biomarkers

The availability of robust non-invasive biomarkers for diagnosis, prediction of response to treatment, and monitoring of disease progression remains a major unmet need. In the most recent systematic review of blood biomarkers (Nisenblat et al., 2016b), the authors identified 141 studies that involved 15,141 participants and 122 biomarkers. They concluded that none of the biomarkers displayed enough accuracy to be used clinically outside a research setting. Disappointingly, most endometriosis biomarker studies were underpowered, had significant methodological issues, or demonstrated a poor choice of control subjects. The failure of these and other studies prompted the development of rigorous guidelines for standardization of data and sample collection by the World Endometriosis Research Foundation (WERF) that have been published in a series of articles that aim to increase in the rigor and reproducibility of investigations (Fassbender et al., 2014; Rahmioglu et al., 2014; Vitonis et al., 2014).

A Cochrane review of the diagnostic accuracy of imaging for endometriosis included 49 studies involving 4,807 women: the evaluation included 13 studies of superficial peritoneal endometriosis, 10 of ovarian endometriomas, and 15 of deep disease (Nisenblat et al., 2016a). The most studied modalities were transvaginal ultrasound and magnetic resonance imaging. Most studies were of poor methodological quality and none of the imaging methods assessed were able to detect endometriosis with enough accuracy that they could be recommended to replace surgical evaluation. A systematic search of PubMed, Embase, NI-15-CRD (including DARE, NHS-EED, and HTA), and the Cochrane Library carried out on September 9, 2020, for this review

failed to identify any new biomarkers introduced into clinical practice since 2016. Recently, there have been some promising leads using blood microRNAs as biomarkers (Moustafa et al., 2020), although this field has previously been undermined by poor reproducibility between studies (Vanhie et al., 2019).

PATHOBIOLOGY OF ENDOMETRIOSIS

Endometriotic lesions: Origins

Endometriosis lesions occur spontaneously in species that menstruate, including higher primates (humans, macaques, and baboons) and some monkeys (cynomolgus). A paper by John Sampson, originally published in 1927, is credited with developing the hypothesis that retrograde menstruation (i.e., the efflux of tissue fragments, cells, and blood via the Fallopian tubes) is equivalent to a "seed" that grows in the "soil" of the peritoneal wall (Horne and Saunders, 2019). Notably, the title of Sampson's paper makes it clear he considered this a possible explanation for "peritoneal disease," and in his extensive investigations of endometrial pathology, he found "shed" cells in the vasculature which may be a more likely mechanism for the formation of deep disease and may explain why endometriosis often occurs in association with adenomyosis (Sampson, 1927). Other theories for the formation of lesions include transformation of peritoneal mesothelium (so called "coelomic metaplasia"), a mechanism that would only explain the presence of lesions on peritoneum but not at other sites (Zondervan et al., 2020).

The classical description of an endometriosis lesion is as a "piece of tissue" that resembles the endometrial lining of the uterus (referred to as the "eutopic endometrium" in studies comparing its phenotype with the ectopic lesions). The eutopic endometrium is a dynamic multicellular steroid-responsive tissue with epithelial cells supported by a stromal compartment containing a rich blood supply and fluctuating populations of immune cells, the luminal portion of which breaks down and is shed during menstruation (Gibson et al., 2020; Wang et al., 2020). Studies on the etiology of endometriosis lesions have benefited from an improved understanding of the regulation of endometrial repair combined with interrogation of primate and rodent models using "menstrual tissue" to generate artificial lesions (Critchley et al., 2020; Saunders, 2020).

Cells liberated from endometrium during menstruation include epithelial cells (glands and luminal), stromal fibroblasts/decidual cells, vascular cells (perivascular and endothelial), and a diverse population of immune cells (notably neutrophils, monocytes/macrophages, and uterine natural killer [uNK] cells) (Armstrong et al., 2017). All these cell types have the potential to contribute to peritoneal lesions providing they can remain viable and evade immune surveillance in the peritoneal cavity. Three cell types have received the most attention: stem/progenitors, stromal fibroblasts, and immune cells. Rare progenitor (stem) cells have been identified in stromal and epithelial compartments of the human eutopic endometrium (Gargett et al., 2016), and stromal cells with clonogenic and multilineage potential have been isolated from menstrual blood (Bozorgmehr et al., 2020). Although progenitor cells may proliferate and contribute to lesions over time, their rarity makes it unlikely they make up a significant proportion of the tissue mass during the initial phases of tissue adhesion, invasion, and proliferation with the more abundant stromal and immune cells playing a key role. Studies comparing the phenotype of stromal fibroblasts from women with endometriosis have identified differences in their behavior including epigenetic changes resulting in an aberrant response to estrogen (Houshdaran et al., 2020). It is likely that the remarkable cell plasticity that has evolved to ensure rapid scarless repair of the endometrial lining in response to the "wound" inflicted at the time of menstruation (including mesenchyme-to-epithelial transformation) contributes to formation of multicellular lesions when the cells are in extra-uterine locations. Parallels between the mechanisms regulating menstruation and those that may support formation of lesions include transient hypoxia (Li et al., 2021), the release of iron, and activation of platelets (Ng et al., 2020; Yan et al., 2020). The other cell types that play a critical role in both menstrual tissue and endometriosis lesions are immune cells that are discussed in more detail below. Peritoneal fluid (PF) also contains a diverse population of immune cells (Guo et al., 2020), and there is compelling evidence from animal models that the immune cells in endometriosis lesions are a mixture of those shed from endometrium and those recruited from the local environment (Greaves et al., 2014b).

Genetic and genomic impacts

Endometriosis is reported to "run in families" with results of twin studies suggesting heritability may be as high as 50% (Saha et al., 2015). Genome-wide association studies (GWAS) using samples from thousands of women based in the United States, Australia, Japan, and Europe (low representation of other nationalities) have identified single gene polymorphisms (SNPs) that appear overrepresented in those with more severe stage of disease (Nyholt et al., 2012; Rahmioglu et al., 2012; Sapkota et al., 2017). Although extensive, these GWAS studies are only powered to investigate the effect of the most common SNPs, and rare polymorphisms require other approaches, such as family-based sequencing. To date, no such rare variants have been reported for endometriosis.

Comparisons to other SNP datasets have detected overlap between the common SNPs associated with endometriosis and other gynecological disorders such as infertility, fibroids, and cancer (Barban et al., 2016; Gallagher et al., 2019; Painter et al., 2018). These associations are perhaps unsurprising, because steroid hormones are implicated in the etiology of all these disorders. Complementing these findings, a meta-analysis of 11 genome-wide association case-control datasets identified five loci significantly associated with endometriosis risk that were close to genes involved in sex steroid hormone pathways (Sapkota et al., 2017). Other pathways and cellular regulators highlighted as a result of genomic studies include the MAP kinase signaling cascade (Uimari et al., 2017), interleukin 1A (a cytokine implicated in inflammatory responses) (Sapkota et al., 2015), WNT signaling (Gallagher et al., 2019), and steroid metabolism (Sapkota et al., 2017). Meta-analysis has also identified shared genetic signatures between migraine and depression with the latter highlighting a link to disturbances in gut mucosa (Adewuyi et al., 2020, 2021).

A limitation of existing GWAS is that interpretation of risk factors and pathways is largely based on "nearest" gene

Table 1. Hormone suppressive drugs used in the treatment of endometriosis

Drug	Mode of administration	Mechanism of action	Recommended length of treatment	Side effects
Combined oral contraceptives	oral (can be taken continuously), patch, or ring	ovarian suppression[a]	long term	nausea, headaches
Progestogens	oral or intramuscular depot injection or intrauterine system or subdermal implant	endometrial regression, some ovarian suppression[b]	long term	weight gain, bloating, acne, unscheduled bleeding (amenorrhea common after prolonged depot use)
Antiprogestogens	oral	ovarian suppression[a]	long term	unscheduled bleeding, estrogen deficiency, masculinization
Gonadotrophin-releasing hormone agonists	subcutaneous or intramuscular injection	ovarian suppression[a]	6 months	vasomotor symptoms, vaginal dryness, sleep disturbance
Gonadotrophin-releasing hormone antagonists	oral	ovarian suppression[a]	6 months	vasomotor symptoms, vaginal dryness, sleep disturbance
Aromatase inhibitors	oral	reduction in aromatase activity in endometriosis lesions	6 months	vasomotor symptoms, decreased libido

[a]Treatment that stops or lowers the amount of estrogen made by the ovaries.
[b]Hormonal management to stop or reduce endometrial cell proliferation and menstrual bleeding.

approaches that do not take account of potential impacts on other genes resulting from changes in long range regulatory elements. Linking GWAS with transcriptional datasets should help narrow down those genes that are most likely to play a role in disease risk. This strategy has been successful in identifying SNPs important for progression of cancers of the breast (Wu et al., 2018) and ovary (Lu et al., 2018). A recent study compared transcriptome-wide differential expression in endometrium from 200+ women (endometriosis versus controls), and after accounting for cyclical tissue changes, the study identified 39 genes that were differentially expressed, five of which co-located with GWAS loci. This result highlights both the potential application of this approach but also the need for more expression quantitative trait locus (eQLT) studies, assessment of distal genes, and larger datasets (Mortlock et al., 2020). This area will continue to be challenging because linking genetic variant perturbance of transcriptomic patterns cannot be limited to lesions but must include eutopic endometrium and cells in PF and blood if we are to advance our understanding of etiology and use this in the design of improved therapies.

The impact of regulatory mechanisms involving epigenetic modifications on the etiology of endometriosis is also a rapidly expanding field. Some of the pathways identified to date overlap with those already found by studying expression of individual genes. For example, Rahmioglu et al. (2017) reported significantly different methylation signatures between endometrium and endometriotic tissue relevant to WNT signaling, and Houshdaran et al. (2020) published several papers documenting aberrant changes in the endometrial DNA methylome resulting in altered response to estrogen.

In the a study using exome sequencing of deep endometriosis, lesions in 24 patients were found to have somatic mutations in genes associated with malignant transformation (Anglesio et al., 2017). Although it has been suggested these mutations might predispose women with endometriosis to develop some forms of cancer, other studies have detected *de novo* somatic mutations in normal endometrial epithelium that increase with age (Lac et al., 2019), and there are no reports that those with deep disease have an excess of cancers compared with other subtypes. These data have prompted a discussion about the developmental trajectories of the different cell types within the lesions as well as the potential impact of mutations on response to therapy (Guo, 2020).

Hormonal regulation

Most papers on endometriosis refer to it as an "estrogen-dependent" disorder, and we suggest this definition should be updated to "steroid-dependent" to reflect the importance of other steroids and their receptors in regulation of cells in both eutopic and ectopic endometrium. To establish a link between endometriosis and steroid hormone action, several lines of enquiry have been pursued including the impact of ovarian endocrine hormones (menstrual cycle) on cell function, evidence for local hormone metabolism within the lesions, and cell-specific patterns of expression of steroid receptors. These observational studies have been complemented by studies using cells/cell lines and animal models to evaluate the impact of steroids on expression of genes implicated in cell proliferation, angiogenesis, neurogenesis, and inflammatory pathways that have improved our understanding of the pathophysiology of endometriosis.

Table 2. Active (recruiting) phase III clinical trials for endometriosis

Drug	Study population	Target/ mechanism (mode of delivery)	Primary outcome	ClinicalTrials.gov NCT identifier
Linzagolix[a] (in combination with addback HRT)	surgical diagnosis of endometriosis (all subtypes)	gonadotropin-releasing hormone antagonist (oral)	pain score (dysmenorrhea and non-menstrual pain)	NCT03992846, NCT03986944
Elagolix[a] (in combination with combined oral contraceptive)	surgical diagnosis of endometriosis (all subtypes); moderate to severe pain	gonadotropin-releasing hormone antagonist (oral)	pain score (dysmenorrhea)	NCT04333576
Dienogest[a]	confirmed or suspected of endometriosis; painful symptoms	progestin (oral)	pain score (overall pain)	NCT04256200
Naltrexone (in combination with norethindrone acetate)	surgical diagnosis of endometriosis (all subtypes); moderate to severe pain	competitive opioid receptor antagonist (oral)	pain score (overall pain)	NCT03970330
DLBS1442 (extract from fruit of native Indonesian plant *Phaleria macrocarpa*)	suspected cystic endometriosis or adenomyosis	anti-angiogenic, anti-inflammatory and anti-apoptotic effects (oral)	composite pain score (dysmenorrhea, dyspareunia, non-menstrual chronic pelvic pain, dysuria, dyschezia)	NCT01942122

[a]Phase III trials exploring improved drug regimens for hormone manipulation and/or suppression.

In the normal endometrium expression of receptors that bind to estrogens (ERα, ERß, and GPER1), androgens (AR), progestins (PRA and PRB), or glucocorticoids (GR and MR) are both cell-specific and menstrual cycle phase-dependent (Gibson et al., 2020; Yilmaz and Bulun, 2019). Disregulation of expression of PR, including altered epigenetic programing of the PR promoter has been detected in endometrium and lesions from women with endometriosis (Yilmaz and Bulun, 2019). These findings are consistent with reports that stromal cells from women with endometriosis are less responsive to the actions of progesterone, so-called progesterone-resistance (Houshdaran et al., 2020), resulting in compromised stromal epithelial cross-talk

Increased expression of ERß in endometriosis lesions and lesion-derived stromal cells has been widely reported (for comprehensive review, see Yilmaz and Bulun, 2019). The availability of ERß-selective agonists prompted their evaluation in endometriosis models with promising results for ERb041, a compound developed by Wyeth (Harris et al., 2005). Clinical trials of ERb041 were conducted in more than 300 women and completed in 2007, however, to date, no details of findings have been reported (Guo et al., 2009). The apparent failure of these trials shows how challenging it is to design therapies that have disease-sparing impacts in a disorder with complex cell-cell interrelationships. For example, whereas ERß agonists can inhibit proliferation of epithelial cells, they stimulate angiogenesis and production of regulatory molecules by endothelial cells derived from endometrial tissue (Greaves et al., 2013, 2014a) and could also affect the function of immune cells including macrophages (Greaves et al., 2015). Although there have been promising results from a new generation of ligands that show strong ER-dependent anti-inflammatory activity in a preclinical mouse model of endometriosis (Zhao et al., 2015) (Table 4), they have not yet progressed to clinical trial.

Another promising avenue for translational medicine has been the discovery that, as in hormone-dependent cancers, lesions exhibit an altered steroid tissue microenvironment (Figure 2). Although ovary-derived bioactive steroids are delivered directly into the lesions after they develop their own blood supply, measurement of steroid concentrations in homogenates of endometriosis lesions using sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) has shown less cyclical variation than in eutopic endometrium (Huhtinen et al., 2012, 2014; Keski-Rahkonen et al., 2013). These results have been explained by increased expression of enzymes that can contribute to *de novo* synthesis of steroids and activation of blood-derived conjugated steroids (Rižner et al., 2017). Expression of aromatase (a key enzyme in biosynthesis of estrogens) in lesion-derived stromal cells was reported more than 20 years ago, and aromatase inhibitors are now being used to treat endometriosis (Table 1). Due to their side effect profile, European (ESHRE) guidelines recommend they are used in combination with other drugs and not as a first line therapy (Dunselman et al., 2014). New

Table 3. Active (recruiting) phase I–II clinical trials for endometriosis

Drug (trial acronym)	Study population	Target/mechanism (mode of delivery)	Primary outcome	ClinicalTrials.gov NCT identifier	Status
V-Endo (derived from hydrolyzed, heat-inactivated, pooled blood of women with endometriosis)	surgical diagnosis of endometriosis (all subtypes); moderate to severe pain	believed to cause immune tolerance to endometriosis and anti-inflammatory effect (oral)	pain score (menstrual)	NCT03340324	phase II-recruiting
Green tea (rich in natural catechins/flavonoids)	ultrasound confirmed endometrioma; moderate to severe pain	anti-angiogenic effects (oral)	endometriosis lesion size (MRI assessment)	NCT02832271	phase II-recruiting
Quinagolide (QLARITY, RAQUEL)	MRI confirmed endometrioma and deep disease	selective dopamine D2-receptor agonist; anti-angiogenic effects (vaginal ring)	endometriosis lesion size (MRI assessment)	NCT03749109, NCT03692403	phase II-recruiting
Cabergoline	surgical diagnosis of endometriosis (all subtypes); moderate to severe pain	selective dopamine D2-receptor agonist; anti-angiogenic effects (oral)	composite pain score (impact of pain on physical function and mood)	NCT03928288	phase II-recruiting
MT-2990	surgical diagnosis of endometriosis (all subtypes); moderate to severe pain	monoclonal antibody targeting IL-33, anti-inflammatory effects (intravenous)	pain score (non-menstrual pain)	NCT03840993	phase II-recruiting
FOR-6219	premenopausal healthy women	hydroxysteroid (17B) dehydrogenase inhibitor; impact on local estrogen production (oral)	safety and tolerability	NCT03709420	phase I-recruiting
Melatonin	surgical diagnosis of endometriosis (all subtypes); moderate to severe pain	anti-oxidant and anti-inflammatory effects (oral)	pain score (overall pain)	NCT03782740	phase II-recruiting
BAY1817080	healthy volunteers	purinergic P2X3 receptor antagonist; anti-neurogenic and anti-inflammatory effects (oral)	pharmacokinetics	NCT04487431, NCT04471337, NCT04454424, NCT04423744	phase I-recruiting

generations of drugs that target other enzymes overexpressed in endometriosis lesions include those directed at 17betaHSD1 (Heinosalo et al., 2019), dual inhibitors of steroid sulfatase/17beta-taHSD (Salah et al., 2017, 2019), and AKR1C3 (Rižner and Penning, 2020). Although a clinical trial for the 17ßHSD inhibitor FOR-6219 is underway (Table 3), trials with the AKR1C3 inhibitor BAY1128688 were terminated early due to reports of hepatotoxicity (NCT03373422).

Angiogenesis, neuro-angiogenesis, and neuro-inflammation

Endometriosis lesions are complex multicellular structures, and vascularization, including the growth of new blood vessels (angiogenesis), plays a critical role in their establishment, survival, and growth (Taylor et al., 2009) (Figure 2). Studies on lesions have benefited from prior knowledge gained from profiling of angiogenic factors, and angiogenic receptors, in human normal endometrium demonstrating high levels of expression of vascular endothelial growth factor (VEGF-A) and neuropillin-1 (NRP-1) as the predominant receptor mRNA (Nap et al., 2004). Hypoxia plays an important role in regulation of gene expression during menstruation (Maybin et al., 2018) and also within the lesion microenvironment where it may stimulate biosynthesis of estrogens and expression of estrogen receptors (Li et al., 2021), the importance of which was detailed in the preceding section.

The repurposing of angiostatic therapies by targeting the vascular endothelial growth factor/tyrosine kinase signaling pathway has been explored as a treatment for endometriosis (Nap et al., 2004), however, because tyrosine kinase inhibitors can induce miscarriage and birth defects, concerns have been expressed about their use in a population who might be at risk of pregnancy (Becker et al., 2017). A more recent review considered the different mechanisms involved in the vascularization of lesions including *de novo* growth (angiogenesis), vasculogenesis, and the formation of interconnected networks, arguing that each of these processes might be targeted separately and combinations of drugs should also be considered (Laschke and Menger, 2018).

The description of a link between the growth of new blood vessels and nerve fibers (i.e., "neuro-angiogenesis") has provided a mechanism that could explain the association between the presence of ectopic tissue and pain pathways (Asante and Taylor, 2011). Increased attention is also being paid to cross-talk

Table 4. Potential therapies for endometriosis that have shown a positive response in mouse models of endometriosis

Target protein	Drug type/name	Model	Results	References
PDK	inhibitor/DCA	mouse (i.p. injection menses-mimic)	reduced lesion size	Horne et al., 2019a
EP2/4	mixture of inhibitors (AH6809/AH23848)	mouse host (xenograft human cells)	decreased lesion size and pain response	Arosh et al., 2015
EP2	antagonist/PF04418948	mouse (i.p. injection menses-mimic)	reduced evoked abdominal pain response	Greaves et al., 2017
TRPV1	antagonist/JNJ17203212	mouse (i.p. injection menses-mimic)	no impact on evoked abdominal pain	Greaves et al., 2017
IL-33	antibody/A10-1C04	mouse (i.p. injection minced uterus)	reduced volume of lesions	Kato et al., 2019
IRAK4 (IL-1R signaling	inhibitor/AS2444697	mouse (i.p. injection minced uterus)	reduced volume when administered 2 weeks after lesion induction	Kato et al., 2019
IL-1ßR	inhibitor/linsitinib	mouse (i.p. injection menses-mimic)	reduced neuronal growth, abrogated spontaneous pain behaviors	Forster et al., 2019
RAMP-1 (CGRP receptor)	antagonist/CGRP8-37	mouse, ectopic endometrial transplant model	inhibition of lesion growth/angiogenesis	Honda et al., 2020
CB1/2	THC (natural agonist)	mouse (suture onto peritoneal wall)	reduced cyst formation, abrogated pain and anxiety behaviors	Escudero-Lara et al., 2020
CB1/2	agonist/WIN 55212-2	nude mice with human cells from deep nodule	reduced volume of implant	Leconte et al., 2010
Estrogen receptors	CLI (ERß) and OBHS (ERα)-selective ligands have anti-inflammatory activity	mouse (suture onto peritoneal wall)	reduced lesion volume, reduced innervation	Zhao et al., 2015
Multiple signaling pathways; ATP?	Niclosamide (FDA-approved helminth treatment)	mouse (suture onto peritoneal wall)	reduced size cysts, reduced cell proliferation	Prather et al., 2016

between nerves and immune cells with "neuro-inflammation" believed to play a role in activation of both central and peripheral pain pathways in endometriosis and it underpins the development of therapies targeting inflammatory and pain pathways described below (Wei et al., 2020).

THERAPEUTIC STRATEGIES FOR ENDOMETRIOSIS IN CURRENT CLINICAL PRACTICE

Therapeutic windows in the life-course of endometriosis

Although there is no cure for endometriosis, research and clinical experience have provided clinicians with a number of strategies for managing its symptoms (Dunselman et al., 2014; Kuznetsov et al., 2017). These can be broadly classified into surgical removal of lesions and a small group of medical therapies, as discussed below. However, unlike cancer, where treating early stage disease typically leads to maximum effect of therapy, it remains difficult to define a "window of opportunity" for treating endometriosis. Specifically, there are currently no recognized treatments that prevent the condition from developing; there is no evidence for a role for medical therapy as an adjuvant to surgery; and it remains unclear how to treat recurrence. Indeed, defining recurrence is a challenge in itself given the lack of accurate non-invasive methods for defining and monitoring disease progression. A recent review used a life-course impact analysis to evaluate the multifactorial impacts of endometriosis, highlighting the need for both early detection but also new approaches to management that are appropriate to stage of life (Missmer et al., 2021).

Surgical removal of lesions

International guideline recommendations for surgical (laparoscopic) removal of all subtypes of endometriosis are based on evidence that laparoscopic treatment improves condition-associated pain (cited as "better or improved") compared to diagnostic laparoscopy alone at 6 months (odds ratio [OR], 6.58; 95% confidence interval [CI], 3.31–13.10) (Duffy et al., 2014). However, this statement is based on data from only three randomized controlled trials (RCT) and a total of just 171 participants with an amalgam of the different subtypes (and data of "moderate quality" when scored using GRADE, a recognized systematic and explicit approach to making judgements about the quality of evidence and strength of recommendations).

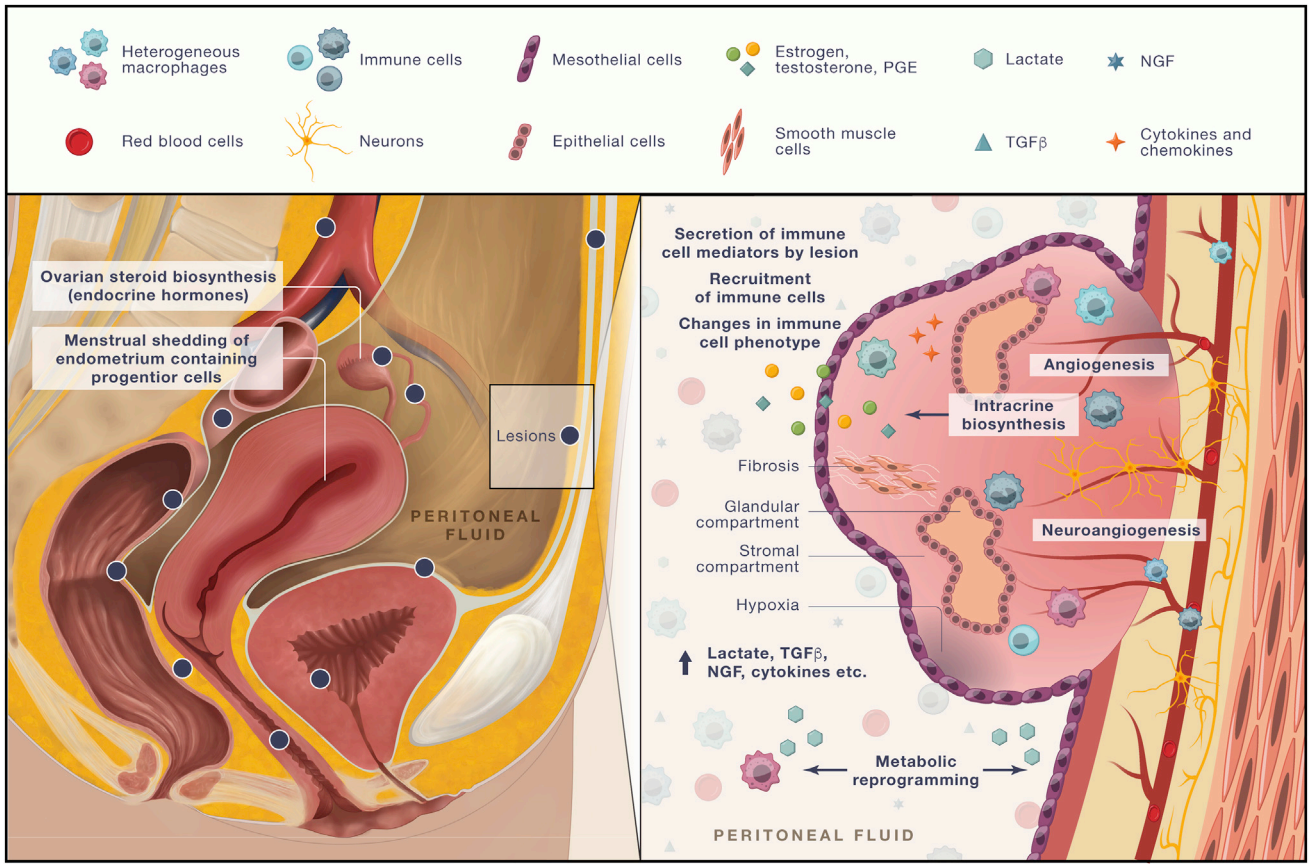

Figure 2. Endometriosis lesions contain a complex mixture of cells and represent a unique specialized microenvironment

(Left) Locations of lesions within the pelvis and other key organs including the bowel, uterus, and bladder. Note the pelvic cavity is lined by mesothelial cells, and the organs are bathed in peritoneal fluid, the constituents of which are altered in women with endometriosis.

(Right) Diagram of a superficial lesion attached to the wall of the peritoneal cavity. Lesions are complex multi-cellular structures with stromal (pink) and epithelial (dotted) compartments, with the former containing fibroblasts, multiple subtypes of immune cells, newly developed blood vessels (angiogenesis), nerves, and regions of fibrosis and hypoxia. Immune cells are recruited to the lesions both from the blood and also from the peritoneal fluid, and their phenotype is influenced by locally high concentrations of steroids and prostaglandins (intracrine synthesis) as well as production of cytokines. Blood vessels and nerves that invade the lesions are found in close proximity (neuroangiogenesis). Mesothelial cells lining the cavity and some macrophage populations produce lactate as a byproduct of metabolism (metabolic reprograming).

Only one RCT included in the analysis has follow-up data to 12 months showing benefit of surgery (OR, 10.00; 95% CI, 3.21–31.17) but this included just 69 participants and is "low quality evidence" using GRADE. Interestingly, a recent update to the review of these data stated that compared to diagnostic laparoscopy only, it is "uncertain whether laparoscopic surgery reduces overall pain" associated with endometriosis (Bafort et al., 2020).

Specifically, there is little scientific evidence to show that surgical treatment of "superficial peritoneal endometriosis" improves overall symptoms and quality of life (QoL) more than not surgically treating the endometriosis, and there are concerns that repeat surgery could exacerbate symptoms. The uncertainty around surgical management of superficial peritoneal endometriosis is compounded by the limited evidence to allow an informed selection of specific surgical modalities to remove the lesions (e.g., laparoscopic "ablation" versus laparoscopic "excision") (Horne et al., 2019b). Surgical excision is, however, generally considered the optimal treatment for "ovarian endometriosis." Whilst medical therapy may be of benefit in managing associated painful symptoms, it does not eradicate ovarian disease (Kuznetsov et al., 2017). No current published data indicate a threshold cyst size below which surgery may be safely withheld in the absence of suspicious ultrasound features, and surgery also means that a tissue specimen can be obtained to rule out unsuspected ovarian malignancy. There is undoubtedly a need for high quality RCTs to compare different surgical treatment approaches for endometriomas (e.g., cyst capsule ablation versus stripping) and to address other unresolved issues such as the potential damage to ovarian reserve either due to the endometrioma itself or as a result of surgical treatment. This has important implications particularly for natural fertility but also for assisted conception.

Although there is a body of evidence to support the effectiveness and acceptability of medical therapy in improving the painful symptoms associated with "deep endometriosis" (Vercellini et al., 2017), surgical treatment to completely excise deep disease is generally considered to be the treatment of choice.

However, the majority of the studies that have reported improvements in QoL following surgical excision of deep endometriosis (typically involving the bowel) have been undertaken using small cohorts of women, usually from single centers, without a comparator arm, affecting the precision and generalizability of the results (De Cicco et al., 2011; Kent et al., 2016; Meuleman et al., 2011).

With regard to endometriosis recurrence, it has been shown that the cumulative probability of persistent endometriosis-related pain following surgical treatment may be as high as 40%–50% by 5 years (Guo, 2009). It is also conceivable that surgical treatment of certain subtypes of endometriosis could exacerbate painful symptoms particularly if this is repeated after relapse. There is increasing awareness of the problem of chronic post-surgical pain (CPSP), which occurs in up to 15%–20% of patients at 3–6 months, and the factors identified as most predictive of CPSP, including other chronic preoperative pain conditions, acute postoperative pain, and comorbid stress symptoms (Simanski et al., 2014; Althaus et al., 2012), are prevalent in women with endometriosis, which raises additional concern.

Current medical management

Hormonal suppressive therapy is routinely prescribed because of the evidence that steroids play a key role in the pathophysiology of endometriosis. Treatments are often started when endometriosis is suspected in young women prior to surgical confirmation of lesions and are also offered after surgery when symptoms do not improve or with recurrent disease. The most commonly prescribed drugs modify the hormonal environment either by suppressing ovarian activity (including secretion of endocrine sex steroids) or acting directly on steroid receptors and enzymes found in the endometrium and lesions (Table 1). They may also reduce menstrual bleeding that will reduce retrograde flow or blunt the triggering of inflammatory pathways implicated in menstrual pain (Laux-Biehlmann et al., 2015). Examples include combined oral contraceptives, progestogens (oral, intramuscular, and intra-uterine system), anti-progestogens, gonadotrophin releasing hormone agonists (GnRH agonists), GnRH antagonists, and aromatase inhibitors (see Table 1). All of these treatments lead to a clinically significant reduction in pain when compared to placebo (when visual analog scales for menstrual and non-menstrual pelvic pain are used in a multivariate network meta-analysis) (Kuznetsov et al., 2017; Taylor et al., 2017). The magnitude of the treatment effect is reported to be similar for all treatments and clinical practice with regards to which drugs are prescribed varies widely. With all drugs targeting hormone pathways, symptoms return after cessation of treatment. Notably, none of the hormone treatments used to manage endometriosis are free of side effects: the contraceptive properties of these drugs may be welcome if the woman does not wish to become pregnant but problematic if fertility is an issue.

Although not recommended in clinical guidelines, moderate-quality evidence shows that the progesterone-receptor modulator, mifepristone, relieves menstrual pain in women with endometriosis, and low-quality evidence suggests that this agent relieves pain with sex, however, cessation of menstrual cycles and hot flashes are common side effects (Fu et al., 2017). In a recent systematic review, the authors considered evidence from the literature published since 1958 that might explain some of the variability in response to progestins and selective progesterone receptor modulators with poor responses in more severe disease (Reis et al., 2020). Danazol (a synthetic androgen), the most commonly used drug to treat endometriosis in the early 1980s, is no longer recommended in clinical guidelines due to its many androgenic side effects (some irreversible), including weight gain, hirsutism and acne, and a tendency to adversely affect blood cholesterol levels (Selak et al., 2007).

Analgesics and neuromodulators

Most women with suspected or known endometriosis who seek pain relief will buy over-the-counter medications such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). However, the evidence that they are effective is of very low quality and based on one older study in only 24 women with endometriosis (Kauppila and Rönnberg, 1985). Evidence that NSAIDs or other COX-2 inhibitors might inhibit ovulation if taken continuously is also of concern if women are hoping to become pregnant (Norman and Wu, 2004).

Neuromodulators are used by pain medicine specialists and primary care physicians in the management of chronic or persistent pain. Neuromodulators differ from conventional analgesics, such as NSAIDs, in that they primarily affect the CNS modulation of pain rather than peripheral meditators of inflammation. Many neuromodulators were originally developed as anti-depressants or anticonvulsants. Tricyclic antidepressants (e.g., amitriptyline and nortriptyline), selective serotonin uptake inhibitors (e.g., duloxetine), and anticonvulsants (e.g., gabapentin and pregabalin) have all shown promise in the treatment of endometriosis. However, in a recent RCT for the management of chronic pelvic pain (in the absence of endometriosis), gabapentin was not proven to be clearly superior to placebo (Horne et al., 2020), and other neuromodulators are sometimes associated with severe, dose-limiting side effects.

Current drug research and development for endometriosis

In light of the negative side effects for many of the commonly used drugs as detailed above, there has been a concerted effort by pharmaceutical companies to develop newer generations of drugs. We have summarized some of the drugs currently under evaluation in phase III and phase I/II trials in Tables 2 and 3, respectively. We have focused on the drugs using pain scores as the primary outcome because this is the symptom that causes the most impact on QoL and for which new medical therapies are most urgently required. Although a number of the phase III trials are exploring improved drug regimens (with predicted fewer side effects) for hormone manipulation and/or suppression including newer formulations of gonadotrophin releasing hormone antagonists and a progestin (marked with *), there are also other trials exploring drugs or plant extracts that target processes such as angiogenesis (DLBS1442, Table 2; green tea, dopamine D2 receptor agonists, Table 3). Trials testing drugs that might have impact on inflammatory or pain pathways are discussed in sections describing those therapeutic targets.

NEW DIRECTIONS IN RESEARCH THAT ARE LEADING TO IMPROVED UNDERSTANDING OF DISEASE PROCESSES AND POTENTIAL THERAPIES

Patients seeking relief from pain symptoms, particularly those who wish to become pregnant, currently have only limited medical treatment options. Researchers recognize this unmet need and have taken advantage of new and emerging information on the pathophysiology of the disorder to rethink their approach to the development of novel therapeutics by targeting processes such as inflammation and angiogenesis or pathways implicated in the generation of painful symptoms. To accelerate access to new drugs suitable for clinical trial, they have also considered parallels between endometriosis and other disorders and opportunities for repurposing of drugs already approved for therapy. Some of these new initiatives are summarized below with drugs showing promise in preclinical animal models highlighted in Table 4.

Endometriosis as an inflammatory disorder

The classification of endometriosis as an inflammatory disorder is based on multiple lines of evidence including reports that the peritoneal environment in women with endometriosis is altered, that endometriosis lesions recruit a large number of immune cells, and that aberrant production of pro-inflammatory regulatory proteins and cytokines (Figure 2) (Horne and Saunders, 2019; Riccio et al., 2018; Zondervan et al., 2020). New insights including evidence of crosstalk between immune cells, nerves, and central pain pathways are also providing opportunities to develop more targeted therapies (Tables 3 and 4).

Endometriosis lesions are often found attached to the peritoneal wall or in association with the ovaries where they are exposed to PF containing immune cells, cytokines, and growth factors (Bain and Jenkins, 2018; Zondervan et al., 2020). Pro-inflammatory factors increased in the PF of women with endometriosis include interleukins (IL-1, IL-6, IL-8, and IL-33), tumor necrosis factor (TNF), and insulin-like growth factor 1 (Cheong et al., 2002; Forster et al., 2019; Kato et al., 2019). Many cells may contribute to this complex mix of factors with different lines of evidence implicating immune cells, mesothelial cells, as well as endometrial tissue arriving in the peritoneum via retrograde menstruation. The full diversity of the immune cell populations in the PF has been revealed using CyTOF, a multiparameter single-cell technique that detected more than 40 different immune cell types within the PF of women, the relative abundance of which was distinct from that of blood (Guo et al., 2020). The study confirmed that the most abundant cell types were cells of the innate mononuclear phagocyte system, however, there were also several populations of adaptive immune cells (T and B cells), as well as rare populations such as mast cells. Although the number of samples interrogated was small (6 controls, 14 women with endometriosis), bioinformatic analysis identified changes in immune cell signatures associated with endometriosis. These included increased numbers of innate immune cells (macrophages and dendritic cells) as well as evidence of increased T cell activation and effector activity (Guo et al., 2020). These new data on T cell phenotype are a valuable complement to studies in mouse models that have recently demonstrated their potential importance in the etiology of the disorder (Xiao et al., 2020). There have been a number of studies highlighting changes in the abundance or phenotype of innate immune cells with a decrease in the phagocytic activity of macrophages combined with increased secretion of pro-inflammatory cytokines, just two of the factors contributing to an altered inflammatory response in women with endometriosis (for review, see Symons et al., 2018). The latest data from analysis of PF of patients being surgically investigated for suspected endometriosis show a good correlation between macrophage phenotype and non-menstrual pain, offering potential that immune cell profiling can be used as a biomarker for pelvic pain (Gibson et al., 2021).

Detailed immunohistochemical analysis of endometriosis lesions from patients has also identified multiple different types of immune cells including the full range of innate and adaptive populations (Zondervan et al., 2020). The lesion-associated immune cells that have received the most attention to date are monocytes/macrophages. Studies on patient samples and fluids complemented by mouse models suggest immune cells recovered from lesions represent a mixture of endometrium-derived populations as well as cells recruited from the peritoneal environment (Greaves et al., 2014b). These studies highlight the critical role immune cells play in promoting angiogenesis (Bacci et al., 2009) and lesion innervation (Bacci et al., 2009; Forster et al., 2019) and suggest that targeting macrophage/monocyte recruitment might offer promise as a way of reducing lesion growth and/or pain symptoms (Bacci et al., 2009; Forster et al., 2019; Hogg et al., 2021).

Other immune cells known to play a role in the function of the eutopic endometrium that are abundant in the tissue at the time of menstruation are neutrophils and uNK, with the latter having a unique $CD56^{+}$ phenotype distinct from NK cells in blood (Armstrong et al., 2017; Drury et al., 2018). A recent paper has reported that systemic circulating neutrophils from endometriosis patients have a different transcriptome compared to neutrophils from healthy controls, and the lesion microenvironment contains factors such as IL-8 that promote recruitment of neutrophils (Symons et al., 2020). Depletion of neutrophils in a syngeneic mouse model of endometriosis reduced concentrations of angiogenic factors such as VEGF in PF and active angiogenesis in lesions (Symons et al., 2020). These results complement and extend findings reported following macrophage depletion opening up new opportunities for endometriosis treatments based on targeting of immune cells with drugs already developed to promote resolution of inflammation (Cartwright et al., 2019). A recent paper suggested numbers of uNK in lesions remain low and the authors speculate this might reflect a failure of the surrounding stromal cells to respond to progesterone and produce factors such as IL-15 (Drury et al., 2018).

Although relatively rare in endometrium and peritoneum, mast cells have attracted particular attention in the context of endometriosis-associated pain (Kirchhoff et al., 2012). Mast cells express estrogen and glucocorticoid receptors and (De Leo et al., 2017) their numbers are increased in ovarian endometriosis lesions and correlate with pain symptoms. There is evidence from *in vitro* studies that E2 may modulate their release of bioactive granules that can stimulate nerve activity, and mast cell stabilizers have been explored as potential therapies for endometriosis-associated pain in preclinical models (Zhu et al., 2019).

Novel therapies targeting endometriosis as an inflammatory disorder

Members of the IL-1 cytokine family (including IL-33 and IL-1β) and their receptors appear to be promising targets for new therapies with evidence from mouse models that monoclonal antibodies directed against these ligands, as well as inhibitors of their MyD88 downstream signaling pathway, can reduce lesion volume (Kato et al., 2019). IL-33 is released by damaged cells and has been implicated in activation of allergic inflammation-related eosinophils, basophils, mast cells, macrophages, and group 2 innate lymphoid cells (IL-C2s) through its receptor ST2 (Chan et al., 2019). One clinical trial is using a monoclonal antibody directed against IL-33 (MT2290; Table 3) replicating an approach that showed promising results in the pre-clinical model. Another exploratory trial (NCT03991520) in 20 women will be testing anakinra, an IL-1 receptor antagonist, used to treat other inflammatory diseases, such as rheumatoid arthritis (Cavalli and Dinarello, 2018). The primary outcome measure is the impact on menstrual pain, and this trial is due to be completed in 2022. A trial using anti-TNF therapy (e.g., monoclonal Infliximab) did not report positive clinical impacts on pain in women with deep endometriosis with no further reports to support their use (Lu et al., 2013).

Prostaglandins are key inflammatory mediators implicated in regulation of processes relevant to endometriosis pathophysiology including angiogenesis, estrogen biosynthesis, and pain symptoms. Therapies targeting both the biosynthetic pathway for prostaglandins, as well as their receptors, have been evaluated. Unfortunately, although upregulation of COX-2 has been widely reported to occur in endometriosis-associated tissues and the CNS (Burney and Giudice, 2012), the use of COX-2 inhibitors is contra-indicated due to their reported side effects on the cardiovascular system. Inhibitors of the enzyme AKR1C3, the overexpression of which is implicated in the metabolism of both steroids and prostaglandins, showed promise in preclinical primate models. Unfortunately, a recent clinical trial was suspended due to hepatotoxicity, highlighting the need for development of more specific inhibitors for this enzyme before it can be retested (Rižner and Penning, 2020). An alternative approach has been to test agonists or antagonists for one or more of the prostaglandin receptors (EP1–EP4). Studies in mouse models have provided promising results including a reduction in evoked pain responses (Arosh et al., 2015; Greaves et al., 2017) (Table 4); future trials are likely to benefit from development of a new generation of highly specific brain-permeable drugs (Amaradhi et al., 2020). Other examples of agents that appeared promising in mouse models and that may be acting by suppressing or modifying inflammatory processes include novel estrogen receptor ligands (Zhao et al., 2015) and the anti-helminth drug, niclosamide (Prather et al., 2016) (Table 4).

Endometriosis as a pain disorder

Research into mechanisms responsible for the chronic pain experienced by women with endometriosis has identified changes in the activity of nerves in both the lesions and the nervous system as well as a close association between nerves and inflammatory cells (see above). Sensory C, sensory Aδ, cholinergic, and adrenergic nerve fibers have all been detected in lesions (Arnold et al., 2012); nociceptive channels including P2X3 are overexpressed in the peritoneal wall and also in endometriosis lesions of women suffering from pelvic pain (Greaves et al., 2014c). Studies in other chronic pain conditions have demonstrated that neuropeptide-expressing small diameter sensory neurons play a key role in generating hyperalgesic responses (Yam et al., 2018) with several neuropeptides identified in these neurons including calcitonin gene-related peptide (CGRP), substance P (SP), and neurokinin. Notably increased expression of CGRP and SP have also been detected in peritoneal endometriotic lesions (Tokushige et al., 2006) and dorsal root ganglia in rodent models of endometriosis. Recent studies have also implicated sensory neuron-derived peptides in promoting a fibrotic response within lesions that is implicated in disease pathology (Liu et al., 2019; Yan et al., 2019) (Figure 2).

Imaging studies investigating the role of the CNS have demonstrated that women with endometriosis-associated pain display decreased gray matter volume in brain regions involved in pain perception, (As-Sanie et al., 2012). Similar to other chronic pain conditions, endometriosis-associated pelvic pain is also associated with altered brain chemistry and function in pain-processing regions (As-Sanie et al., 2016). Together, these findings support the role for central pain amplification in the pain process in endometriosis and demonstrate a need for further research into the use of neuromodulator drugs that target central pain dysfunction in women with the condition.

Novel therapies targeting endometriosis as a pain disorder

A link between pain and the altered local steroid microenvironment has also been reported, with evidence that E2 increases expression of nociceptive ion channels such as TRPV1 in lesions in a mouse model (Greaves et al., 2014c; Greaves et al., 2015). It has been postulated that the increased expression of TRPV1 detected in ectopic endometrium may integrate multiple signals to promote pain (Liu et al., 2012), however, studies with a TRPV1 inhibitor were disappointing (Table 4). The potential use of TRPV1 inhibitors is further undermined by clinical trials reporting hyperthermia and thermo-hypoesthesia as major side effects (Damann et al., 2020).

A study using a novel delivery system reported that a P2X3 receptor antagonist (A-317491) accumulated in lesions in a rat model of endometriosis and this resulted in reduction in both mechanical and heat hyperalgesia (Yuan et al., 2017). Although P2X3 is a promising target, antagonists often have poor pharmacokinetic properties, and it is notable that current trials in healthy volunteers are addressing this issue using a new compound (BAY1817080; Table 3). Some drugs have also been repurposed following reports that they are effective in the treatment of other inflammatory pain and neurological conditions including migraine and arthritis. Notably, calcitonin gene-related peptide receptor (CGRP) has been widely studied as a target for treatment of migraine-associated pain (Blumenfeld et al., 2020; Edvinsson, 2018). Two types of CGRP inhibitors have been developed—monoclonal antibodies (Israel et al., 2018) and CGRP receptor antagonists (Holland and Goadsby, 2018)—with the former approved in the United Kingdom as treatments for migraine. A recent clinical phase IIb/III trial using Atogepant, an orally administered, small-molecule, CGRP antagonist,

reported that it was safe and well-tolerated and reduced attacks of migraine (Goadsby et al., 2020). An inhibitor of the CGRP receptor RAMP-1 has shown promising results in a preclinical model of endometriosis (Honda et al., 2020) (Table 4), however, to date, there are no clinical trials for any of these drugs in endometriosis patients.

Natural cannabinoids (isolated from cannabis plants) are widely used a self-administered therapy for chronic pain including pain experienced by patients with endometriosis. Cannabinoids activate G protein coupled receptors CB1 and CB2 that are expressed in cells that play a critical role in the relay and modulation of pain pathways (Pertwee, 1997). CB1 receptors are reported to contribute to lesion growth in a mouse model (Sanchez et al., 2017). CB2 receptors are expressed by immune cells and in the nervous system and have been co-localized with TRPV1 receptors in injured nerve fibers (Anand et al., 2008). The impact of natural and synthetic agonists of the CB1 and CB2 receptors have been explored in preclinical models of endometriosis with some promising results reported (Escudero-Lara et al., 2020; Leconte et al., 2010; Sanchez et al., 2012) (Table 4). Two trials using cannabinoid extracts to treat pain in women with endometriosis have recently been listed on ClinicalTrials.gov (NCT03875261; NCT04527003); there are no trials listed with receptor-selective agonists of the kind used in preclinical models, which is disappointing.

An alternative strategy may be to directly target the nerves involved in the pain pathways. For example, injections of neurotoxin (Onabotulinum) have been used to treat women with chronic pelvic pain associated with myofascial pelvic pain (MFPP) syndrome with 74% of patients reporting an improvement in symptoms (Jha et al., 2020). A link between the chronic pelvic pain experienced by women with endometriosis and myofascial trigger points has been proposed, opening up a new therapeutic target (Aredo et al., 2017).

Endometriosis as a metabolic disorder

Endometriosis exhibits cancer-like features, and both endometriosis and cancer can be considered as metabolic disorders (Coller, 2014; Young et al., 2014). For example, tumor cells are programmed by transforming growth factor β1 (TGF-β1) to use aerobic glycolysis, resulting in increased secretion of lactate (Hirschhaeuser et al., 2011). TGF-β1 and lactate are both elevated in the PF of women with endometriosis, and this is paralleled by a switch from normal mitochondrial respiration toward glycolysis in the peritoneal mesothelial cells (HPMCs) that line the pelvic cavity (Young et al., 2017). In tumors, lactate is considered a key factor in driving cell invasion, angiogenesis, and immune suppression (Hirschhaeuser et al., 2011), processes that are also implicated in the establishment and survival of endometriosis lesions. As noted in previous sections, macrophages are the most abundant immune cell within the peritoneal cavity; changes in macrophage phenotype (polarization) are accompanied by major changes in metabolism with those considered proinflammatory relying on glycolysis, whereas anti-inflammatory (so-called M2) macrophages are more dependent on oxidative phosphorylation (for review, see Viola et al., 2019). The metabolic state of macrophages has received less attention in endometriosis than in cancer (Mehla and Singh, 2019); however, with many studies showing their polarization state may be altered in endometriosis, their contribution to changes in the abundance of metabolites in PF and blood merits further study. Quantifying differences in serum metabolites found in women with and without endometriosis is also an active area of investigation. A recent pilot study reporting the use of proton-nuclear magnetic resonance-based analysis was able to detect differences between patients with ovarian and deep disease (Maignien et al., 2020). Studies on serum metabolites are also being used to explore links between the microbiome and pain pathways that have been described in other conditions (Kang et al., 2019; Onuora, 2020).

Novel therapies for endometriosis based on targeting metabolic endpoints

Peritoneal mesothelial cells from women with endometriosis exhibit a greater dependence on energy production through glycolysis than those of women who are disease-free (Horne et al., 2019a). This abnormal cellular energy state can be corrected by treatment with the small-molecule drug dichloroacetate (DCA) a pyruvate dehydrogenase kinase (PDK) inhibitor used to treat cancer (Sutendra and Michelakis, 2013). Notably, we have demonstrated that DCA can reduce peritoneal mesothelial cell lactate release *in vitro*, and oral dosing of mice with induced endometriosis reduces lesion size *in vivo* (Horne et al., 2019a) providing an excellent example of drug repurposing (Table 4). To translate these results to women, we are using DCA in an exploratory-phase clinical trial (EPiC; ClinicalTrials.gov identifier NCT04046081). If effectiveness and acceptability are demonstrated, DCA could offer real potential as a new non-hormonal treatment for women with endometriosis.

Strategies for symptom management based on dietary supplements and natural products

Supplements, such as Omega-3 polyunsaturated fatty acids (O-PUFAs), have been investigated as a way of reducing inflammation and pain. O-PUFAs play a role in the regulation of prostaglandins and cytokines by competing with Omega-6 PUFA to produce anti-inflammatory lipid mediators (Calder, 2015). Intake of food with a high content of O-PUFA has been shown to have an anti-inflammatory effect in conditions such as atherosclerosis (Hino et al., 2004). In rat models of endometriosis, O-PUFA reduced lesion size and local prostaglandin/cytokine production (Netsu et al., 2008) and omega-6/3 and omega-9/6 decreased pain but had no impact on fertility (Pereira et al., 2019). In a study of 42 young women (15–18 years of age), fish oil supplementation was reported to significantly reduce menstrual pain (Harel et al., 1996). Results from trials in women with painful endometriosis have been less clear cut; in a pilot trial comparing women taking 1,000 mg O-PUFA with 1,000 mg olive oil for 8 weeks, there were no adverse effects but the study was underpowered for efficacy (Abokhrais et al., 2020). In a study focused on 147 young women (12–25 years of age) who were assigned to groups taking vitamin D, 1,000 mg O-PUFA, or placebo for 6 months, the change in pain scores was not statistically significant and there was improvement in the placebo group (Nodler et al., 2020). Further properly powered RCTs are required, and the impact of placebo on pain perception needs to be considered before we can be sure O-PUFA offers real clinical benefit.

Natural products, most notably those considered having anti-inflammatory or anti-angiogenic qualities, are also being increasingly considered as therapies for endometriosis. Examples include Resveratrol (grapes/berries), curcumin derived from the roots of *Curcuma longa* (turmeric), (Vallée and Lecarpentier, 2020), and compounds found in green tea (Xu et al., 2011). Although Resveratrol was reported to reduce lesion size in a pre-clinical model of endometriosis (Bruner-Tran et al., 2011), in a subsequent RCT, it was not superior to placebo for treatment of pain (44 women) (Mendes da Silva et al., 2017). Curcumin has been widely reported to exhibit anti-inflammatory properties in a wide range of human and animal studies including models of endometriosis (Vallée and Lecarpentier, 2020). A recent paper explored the use of carbon nanofibers as a delivery system for prolonged release of curcumin within the peritoneum reporting positive results with reduction in glands, stroma, and invasion of immune cells in a mouse model (Boroumand et al., 2019). Curcuma capsules (Flexofytol) are currently being used in an exploratory clinical trial (NCT04150406, ENDOFLEX) in 54 women with evaluation of change in pain score after 4 months as the primary outcome: the trial is due to be completed at the end of 2021. Green tea is a popular drink considered to have potent antioxidative, antimitotic, and antiangiogenic properties; one of the active compounds in green tea is epigallocatechin-3-gallate (EGCG) (Nagle et al., 2006). EGCG has been shown to inhibit angiogenesis and suppress the VEGFC/VEGFR2 signaling pathway in a mouse model of endometriosis (Xu et al., 2011). A green tea extract (green tea extract SUNPHENON EGCg) is currently being evaluated in a randomized double-blind trial (NCT02832271) with plans to recruit 185 women with ultrasound-confirmed endometriosis; the primary outcome is lesion size but pain scores will also be taken (Table 3). A newly published review considered a wide range of plant products, including Chinese herbal medicines, and the evidence that they can be used for symptom relief. The authors concluded that although several of them show promise, there was a need for improved standardization, barriers to patentability may limit the incentives to conduct clinical trials, and they are unlikely to be used as a stand-alone therapy (Meresman et al., 2021).

CONCLUSIONS

In the last 10 years, there has been a huge increase in the volume of research into endometriosis, and new ideas are bringing us closer to a fuller understanding of why some, but not all, women develop symptomatic disease. Although we have yet to identify a clinically useful non-invasive biomarker to diagnose disease or serve as a readout in clinical trials of new therapies, there is real hope of a breakthrough in the next 5 years. Notably, the establishment of globally harmonized endometriosis protocols for clinical data and human tissue collection (Fassbender et al., 2014; Rahmioglu et al., 2014; Vitonis et al., 2014) represent an important step toward realizing this goal. There are also hopeful signs that the biomarker field may be able to capitalize on new insights being gained from genomic studies including those on miRNAs (Moustafa et al., 2020) with other novel approaches to biomarker evaluation focusing on low molecular metabolites, with changes in alanine being the most promising (Dutta et al., 2018).

Researchers have tried to increase the range of drugs available for clinical trial in women with endometriosis by considering repurposing of drugs already approved for other painful inflammatory conditions. This strategy has already shown some promising results. For example, immunotherapy either by targeting T cells or administration of immune checkpoint inhibitors has emerged as a promising treatment for chronic inflammatory diseases such as rheumatoid arthritis (Wei et al., 2020) and difficult-to-treat cancers. As our understanding of the role(s) of T cells and other immune cells in the etiology of endometriosis expands, we may soon be able to capitalize on the remarkable progress made by developing and implementing immunotherapy as an endometriosis treatment (Santoso et al., 2020). Our own work that identified the mechanisms responsible for the altered metabolic phenotype of the peritoneal mesothelial cells in women with endometriosis has allowed us to investigate the repurposing of drugs that have impact on lactate production (Horne et al., 2019a). Although preclinical models have been used to support drug development pipelines and drug repurposing, there is still room for improvement with most models only applicable to the early stages of the disease process, an overemphasis on application of techniques to measure evoked rather than spontaneous pain, and very few models of ovarian/deep disease or endometriosis-associated infertility (Saunders, 2020).

Women with endometriosis frequently report beneficial effects from dietary modification on their pain experience, however, evidence for a correlation between particular foodstuffs and macro- or micronutrients remains of low quality (Huijs and Nap, 2020). The emergence of strong and convincing evidence of a link between diet, the microbiota, and the development of chronic pain symptoms in a number of disorders, including those associated with neuroinflammation, has opened up a new and exciting avenue for investigation (Guo et al., 2019; Martin et al., 2018). To date, this topic has received surprisingly little attention among endometriosis researchers (Laschke and Menger, 2016) and now seems an ideal time to use the latest analytical methods to fully explore the link between diet and pain symptoms in women with endometriosis (Lin et al., 2020) and to develop robust evidence to inform patients about the most appropriate nutrition.

In conclusion, the range of new therapies under test is incredibly exciting and offers hope that our goal of designing personalized treatment plans is attainable. We envisage that the focus of these treatment plans will be on the control of symptoms and include options for lifestyle modification (diet/exercise/meditation) and drugs for pain that do not limit fertility, combined with surgery. We strongly believe that these efforts are more likely to succeed now that endometriosis researchers have started to work with non-traditional research partners, such as pain biologists/specialists and data scientists, to better understand this complex disorder so that new knowledge can be applied for patient benefit.

DECLARATION OF INTERESTS

P.T.K.S. declares no competing interests. A.W.H. has consulted for Ferring, Roche Diagnostic, Nordic Pharma, and Abbvie; fees were paid to the University of Edinburgh.

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