Thieme

The Hallmarks of Endometriosis

Markenzeichen von Endometriose

Authors
Iason Psilopatis[1], Stefanie Burghaus[1], Katharina Au[1], Louisa Hofbeck[1], Lisa Windischbauer[1], Laura Lotz[1], Matthias W. Beckmann[1]

Affiliations
1 Department of Gynecology and Obstetrics, Erlangen University Hospital, Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany

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70469 Stuttgart, Germany

Correspondence
Prof. Dr. med. Matthias W. Beckmann
Department of Gynecology and Obstetrics
Erlangen University Hospital, Friedrich Alexander University of Erlangen-Nuremberg
Universitätsstraße 21–23
91054 Erlangen, Germany
matthias.beckmann@uk-erlangen.de

ABSTRACT

A heuristic tool called “the hallmarks of cancer” helps to reduce the enormous complexity of cancer phenotypes and genotypes to a preliminary set of guiding principles. Other aspects of cancer have surfaced as possible improvements in our understanding of the disease’s mechanisms. Endometriosis is a gynecological disease condition negatively impacting the quality of life of many women. To date, there is no curative treatment for endometriosis. Therapy is aimed at treating the symptoms using hormone therapy, pain therapy and complementary therapy. Chronic pain and overlapping pain syndromes and illnesses can also be treated with multimodal pain therapy and psychosomatic therapy. Endometriosis is, however, a chronic and complex entity which, in this regard, resembles cancer. The present work investigates the hallmarks of endometriosis with a view to summarizing the current research status and paving new ways for future research projects.

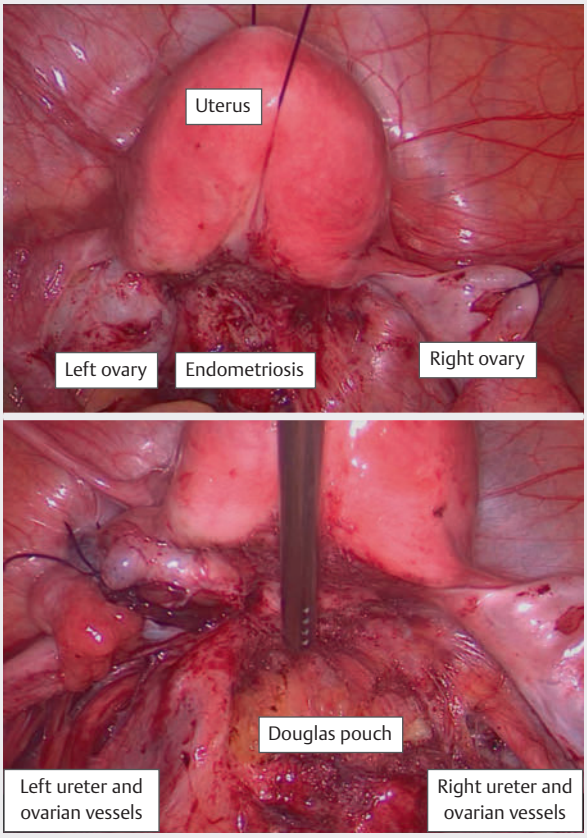
ZUSAMMENFASSUNG

Ein heuristisches Werkzeug, „Markenzeichen von Krebs“ genannt, wird eingesetzt, um die große Komplexität der Phänotypen und Genotypen von Krebszellen zu vereinfachen und in einer vorläufigen Reihe von Leitprinzipien zusammenzufassen. Andere Aspekte von Krebserkrankungen sind in jüngster Zeit auch als potenzielle Ansätze zur Verbesserung des Verständnisses von Krebserkrankungsmechanismen in Erscheinung getretten. Die Endometriose ist eine gynäkologische Erkrankung, welche die Lebensqualität vieler Frauen stark beeinträchtigt. Es gibt bisher keine kurative Behandlung dafür. Die aktuellen Therapien fokussieren darauf, Symptome anhand von Hormontherapie, Schmerztherapie sowie komplementären Therapien zu lindern. Chronische Schmerzen und überlappende Schmerzsyndrome und Erkrankungen können mithilfe multimodaler Schmerztherapien und psychosomatischer Therapien behandelt werden. Aber die Endometriose ist eine chronische und komplexe Entität, die Ähnlichkeiten mit Krebs aufweist. Diese Arbeit untersucht die Kennzeichen von Endometriose mit dem Ziel, den aktuellen Forschungsstand zusammenzufassen und neue Wege für künftige Forschungsprojekte zu ebnen.

Introduction

Endometriosis classification

Endometriosis describes a disease characterized by the colonization of endometrium-like lesions outside the uterine cavity. Ectopic lesions were thought to represent solely lesions on the peritoneum of the internal genital organs (endometriosis genitalis externa), but in the meantime a migration of endometrial-like cells into the myometrium has been also described, hence rendering adenomyosis uteri (= endometriosis genitalis interna) a distinct disease entity. However, since endometriotic lesions may also infiltrate deeply into organs (mostly bowel, bladder or ureter) (deep infiltrating endometriosis) or even spread to the diaphragm or the umbilicus (extragenital endometriosis), symptoms are often extremely complicated [1]. A clinical/intraoperative distinction is made between the following four major entities of endometriosis depending on localization and extent: superficial, ovarian, uterine and deep infiltrating endometriosis. Deep infiltrating endometriotic lesions exceed the surface (usually the peritoneum) and invade into neighboring tissue or organs with an infiltration depth of at least 0.5 cm (▶ **Fig. 1**) [2, 3]. The most widely used clinical/intraoperative classification is the rASRM score, the revised classification of the American Society for Reproductive Medicine (formerly the American Fertility Society) [2, 4]. The rASRM score describes peritoneal and ovarian endometriosis. Deep endometriosis is included in the calculation of the numerical value, but no mapping or classification can be derived from it. To remedy this deficiency, a German-speaking working group has developed the Enzian classification. This classifies deep lesions in 3 anatomical levels or compartments (A: rectovaginal septum/vagina, B: sacrouterine ligament/pelvic wall, C: rectum). #Enzian represents since 2021 a novel comprehensive classification that included the superficial endometriosis, ovarian and with the Enzian classification, hence constituting a more rounded classification system, which, nevertheless, does not incorporate the two major symptoms of endometriosis: pain and infertility [5].



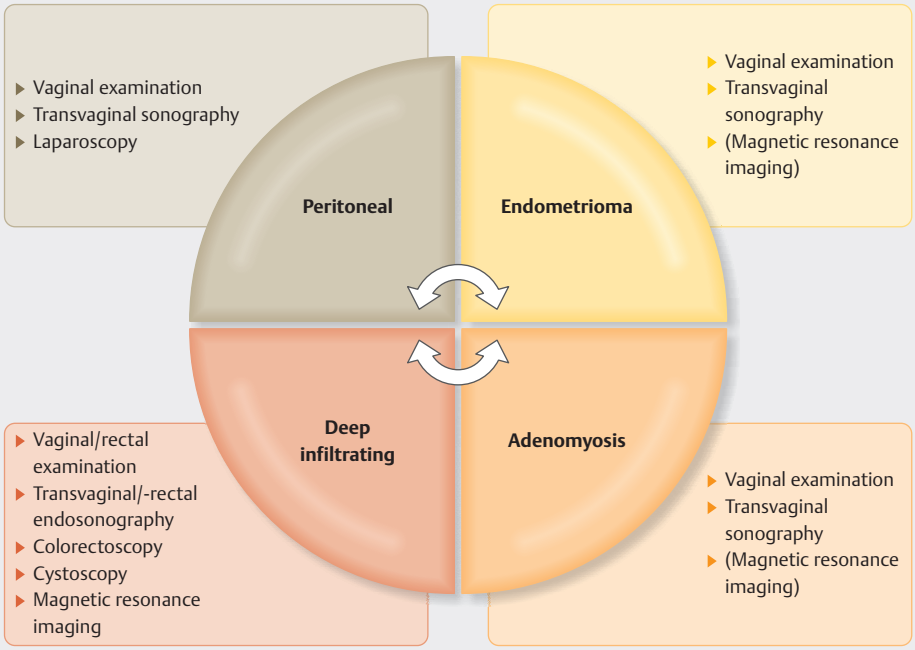
▶ **Fig. 1** Deep infiltrating endometriosis-Intraoperative laparoscopic views (Patient collective-Department of Gynecology, University Hospital of Erlangen).

Symptoms and diagnosis

Diagnosis of endometriosis is based on a detailed medical history, a thorough gynecological clinical examination including vaginal and rectovaginal or rectal palpation, a transvaginal and/or even transrectal sonographic evaluation, a renal ultrasonography with a view to ruling out asymptomatic urinary retention caused by deep infiltrating endometriosis of the ureter, magnetic resonance imaging, as well as a histological examination [6, 7, 8]. The diagnosis of a deep infiltrating endometriosis is mainly clinical – by describing the clinical symptoms (although not specific), inspection with two-leaf specula and vaginal and rectal palpation. Vaginal sonography should be performed first as an imaging measure, not least because of the simultaneous possibility of identifying ovarian endometriomas. Furthermore, deep rectal infiltration can be easily diagnosed by an experienced physician. If rectal endometriosis is suspected, an endosonography and/or colorectoscopy is often automatically arranged. However, endometrial infiltration of the mucosa is rather rare. A colorectoscopy should be performed in the presence of intestinal bleeding and whenever a bowel resection is intended in the case of suspected bowel infestation in order to rule out primary bowel pathologies such as polyps, tumors or inflammatory bowel diseases [9]. ▶ **Fig. 2** summarizes the possible diagnostic approaches based on the four major endometriosis entities. Taken altogether, endometriosis genitalis (including vaginal endometriosis) is mainly associated with dysmenorrhea and dyspareunia, deep infiltrating endometriosis correlates with dysuria and dyschezia, while extragenital endometriosis (in organs other than the bladder or the bowel) requires a symptom-oriented examination [6, 7, 8, 9, 10]. Importantly, superficial peritoneal endometriosis might remain obscure until the performance of a diagnostic laparoscopy.

Current therapeutic standards

Conservative options include medical and complementary procedures, reproductive medicine measures as well as multimodal pain management models (i.e. heat application, physical exercises, etc.) and psychotherapy in the wider context of the bio-psycho-social model. Surgical options include organ-preserving or radical and, if necessary, interdisciplinary ablation or excision of endometriosis lesions, preferably in certified endometriosis facilities

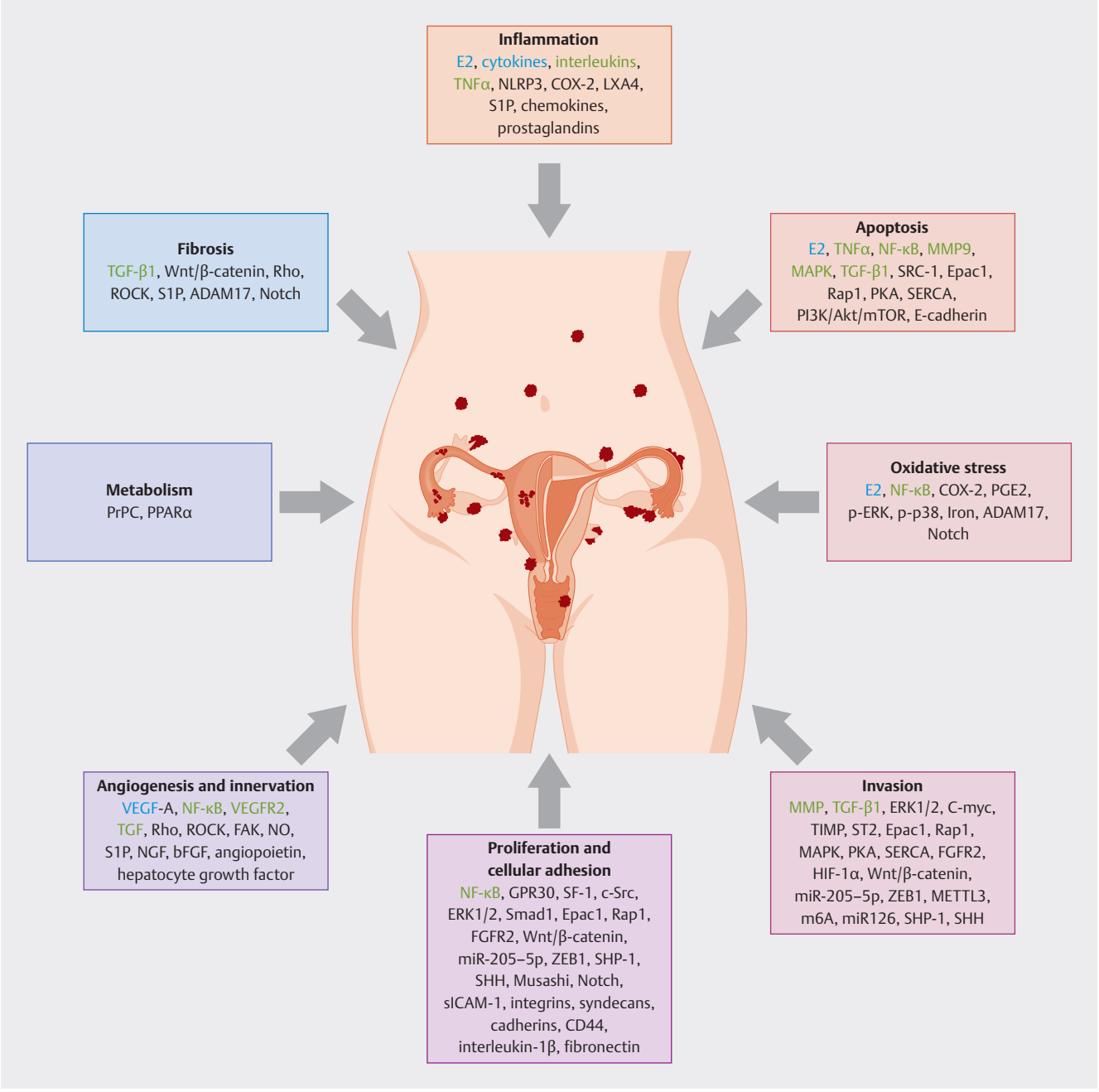


▶ **Fig. 2** Diagnostic approaches based on the four major endometriotic entities.

[11]. Established pharmacologic approaches include either analgesics from the group of non-steroidal anti-inflammatory drugs (NSAIDs) or hormone therapy. NSAIDs pursue a symptomatic therapeutic approach [12]. As non-hormonal options treat purely symptomatically, hormone therapy is generally used. Established hormonal options include progesterons in the first-line therapy, as well as oral contraceptives and Gonadotropin-Releasing Hormone (GnRH) (ant-)agonists in the second-line therapy. There are no objectifiable differences with regard to the reduction of typical pain symptoms. There are differences in terms of undesirable side effects, the duration of possible use and the costs. Drug therapy is only effective while it is being taken, after which symptoms may recur immediately [13]. Progestogens (especially dienogest 2 mg) are the options for first-line therapy. They produce hypoestrogenism through anovulation. In oral contraceptives, they are part of a fixed combination of ethinylestradiol or estradiol valerate. When selecting progestogen, secondary treatment goals such as the treatment of skin blemishes can also be taken into account. Long-cycle use is more effective than cyclical use in reducing symptoms typical of endometriosis and should be favored [11, 13, 14, 15].

Hallmarks of Endometriosis

Over the past years, the scientific community has been able to investigate different molecular pathways and gain an insight into the (epi-)genetic and/or cellular mechanisms that seem to play a significant role in the genesis and progression of endometriosis. Of utmost significance, these pathomechanisms seem to pave new ways in the context of endometriosis diagnosis (as biomarkers) and therapy (as drug targets). The (epi-)genetic mechanisms are involved in the immunologic, immunohistochemical, histological, and biological aberrations of endometriosis [16]. Pelvic endometriosis has a complex pathogenesis and pathophysiological features. Two possible causes of the endometriotic lesions are in situ coelomic metaplasia of the peritoneal lining and transplantation of endometrial tissue through retrograde menstruation. In cases of extrapelvic lesions, vascular or lymphatic metastasis most likely happens infrequently. Through interacting molecular mechanisms that support cellular adhesion and proliferation, systemic and localized steroidogenesis, localized inflammatory response and immune dysregulation, as well as vascularization and innervation, superficial and deep endometriotic lesions seem to be established and maintained [17]. Endometriosis-related signaling pathways included estrogen-2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK), extracellular-signal regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3 K), protein kinase B (PKB/AKT) and mechanistic target of rapamycin (mTOR) (PAM), yes-associated protein (YAP), Wnt/β-catenin, Rho-associated protein kinase (ROCK), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), nitric oxide (NO), iron, cytokines and chemokines [18]. Despite being a benign condition, endometriosis exhibits malignant traits such as metastasis, hyperplasia, and cell invasion. This suggests a possible connection between endometriosis and particular signaling molecules and pathways that influence the invasion and metastasis of numerous common malignancies. The six biological abilities that are acquired throughout the multi-step development of human tumors are the hallmarks of cancer. The defining multiple characteristics provide a framework for understanding the complexity of neoplastic disease. The ability to maintain proliferative signaling, avoid growth suppressors,



▶ **Fig. 3** Hallmarks of endometriosis and their potential targets for therapy. Captions in blue: completed clinical trials. Captions in green: ongoing clinical trials. Captions in black: experimental models in vitro/in vivo. Abbreviations: ADAM17 = A Disintegrin and Metalloprotease 17; COX-2 = Cyclooxygenase 2; E2 = Estrogen 2; EPAC1 = Exchange Protein Directly Activated by cAMP 1; ERK = Extracellular Signal-regulated Kinase; FAK = Focal Adhesion Kinase; FGFR2 = Fibroblast Growth Factor Receptor 2; GPR30 = G Protein-coupled Receptor 30; HIF = Hypoxia-inducible Factor; LXA4 = Lipoxin A4; MAPK = Mitogen-activated Protein Kinase; METTL3 = Methyltransferase-like 3; miR = micro RNA; MMP = Matrix Metallopeptidase; NF-κB = Nuclear Factor kappa B; NGF = Nerve growth factor; NLRP3 = NLR Family Pyrin Domain Containing 3; NO = Nitric Oxide; PGE2 = Prostaglandin E2; PKA = Protein Kinase A; PI3 K/Akt/mTOR = Phosphatidylinositol 3-kinase/Protein Kinase B/mammalian Target of Rapamycin; PPAR = Peroxisome Proliferator-activated Receptor; PrPC = Cellular Prion Protein; Rap1 = Ras-associated Protein-1; ROCK = Rho-associated Protein Kinase; S1 P = Sphingosine-1-Phosphate; SERCA = Sarcoplasmic/endoplasmic Reticulum Ca2+-ATPase; SF = Steroidogenic Factor; SHH = Sonic Hedgehog; SHP-1 = Src Homology Region 2 Domain-containing Phosphatase-1; sICAM-1 = soluble form of intercellular adhesion molecule-1; SMAD = Suppressor of Mothers against Decapentaplegic; SRC = Steroid Receptor Coactivator; TGF = Transforming Growth Factor; TIMP = Tissue Inhibitor of MMP; TNF = Tumor Necrosis Factor; VEGFR = Vascular Endothelial Growth Factor Receptor; ZEB1 = Zinc Finger E-Box Binding Homeobox 1

▶**Table 1** Completed registered clinical trials on the role of signaling pathways in endometriosis.

Agent	Pathway	Completed Clinical trial
Relugolix Triptorelin Linzagolix ASP1707 FOR-6219 Leuprolide Elagolix Sufugolix MK-8342B Progesterone/ Estradiol GnRH-agonist	E2	NCT03204331 NCT03204318 NCT03654274 NCT03232281 NCT03992846 NCT01767090 NCT03709420 NCT02807363 NCT00797225 EudraCT Number: 2004–003829–28 EudraCT Number: 2004–001721–13 EudraCT Number: 2012–002791–14 EudraCT Number: 2012–002449–40 EudraCT Number: 2010–019287–37 EudraCT Number: 2013–003788–67 EudraCT Number: 2015–004326–34 EudraCT Number: 2015–004325–14 EudraCT Number: 2013–000993–32
Ezetimibe Quinagolide	VEGF	NCT04844996 NCT00625950 EudraCT Number: 2018–000915–26
Anti-TNFα	Cytokines	NCT00604864

Abbreviations: E2 = Estrogen 2; VEGF = Vascular Endothelial Growth Factor

▶**Table 2** Ongoing registered clinical trials on the role of signaling pathways in endometriosis.

Agent	Pathway	Clinical trial
Anastrazole plus GnRH agonist	Hormonal	Phase 4 NCT01769781
Danazol	Hormonal	Phase 4 NCT05697471
Resveratrol	Regulation of antioxidant enzymes, TNFα-mediated cytokines	Phase 4 NCT02475564
Vitamin D3 and fish oil	Anti-inflammatory	Phase 4 NCT02387931
Quinagolide	Dopaminergic, VEGF/VEGFR2	Phase 4 NCT03692403
DLBS1442	Anti-inflammatory, antiangiogenic, and apoptosis-inducing	Phase 3 NCT01942122
Pentoxifylline	VEGFC and VEGFR2	Phase 3 NCT00632697
Cabergoline	Dopaminergic	Phase 2 NCT02542410
Botulinum toxin	Neurotoxic	Phase 2 NCT01553201
Gefapixant	P2 X3 receptor antagonist	Phase 2 NCT03654326
Vilaprisan	Selective progesterone receptor modulator	Phase 2 NCT03573336
Epigallocatechin gallate	TGF-β1-stimulated activation of MAPK and Smad pathway, VEGFC-mediated c-JUN, IFN-γ, CXCL3, and MMP-9 pathway	Phase 2 NCT02832271
Melatonin	Caspase, Radical scavenging activity	Phase 2 NCT03782740
MT-2990	Fully human anti-interleukin-33 monoclonal antibody	Phase 2 NCT03840993
Curcumin	p53/NF-κB, IκKα/β, STAT3, and JNK	Recruiting NCT03016039

Abbreviations: CXCL3 = Chemokine Ligand 3; GnRH = Gonadotropin-Releasing Hormone; IFN = Interferon; JNK = c-Jun N-terminal kinase; MAPK = Mitogen-Activated Protein Kinase; MMP = Matrix-Metallo-protease; NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3 = Signal transducer and activator of transcription 3; TNFα = Tumor Necrosis Factor-α; VEGFR = Vascular Endothelial Growth Factor Receptor; TGF = Transforming Growth Factor

withstand cellular death, permit replicative immortality, trigger angiogenesis, and initiate invasion and metastasis are a few of them. These hallmarks are underpinned by inflammation, which supports several hallmark functions, and genome instability, which produces the genetic diversity that speeds up their acquisition. Two newer hallmarks of potential generality include reprogramming of energy metabolism and immune escape [19]. In this regard, ▶ **Fig. 3** summarizes the corresponding hallmarks of endometriosis.

Current (Pre-)Clinical Trials Investigating the Hallmarks of Endometriosis

In 2016, the kinase signaling pathways in endometriosis were investigated and it was concluded that the three main pathways to be targeted for treatment purposes are the IKKβ/NFκB, the MAPK, and the PI3 K/AKT/mTOR pathway [20]. The literature on medications that specifically target the molecular and signaling pathways involved in the pathophysiology of endometriosis was thoroughly reviewed. The discussion included possible therapeutic targets, the molecules upstream and downstream that exhibit critical aberrant signaling, and the regulatory pathways that facilitate the expansion and maturation of endometriotic tissues and cells [21]. Recently, Shi also examined angiogenesis, lymphangiogenesis, neurogenesis, progesterone resistance, genetic alterations, estrogen-dependent induction of inflammation, imbalances in proliferation and apoptosis, and tissue remodeling in the pathogenesis of endometriosis. Additionally, the pharmacological mechanisms, constitutive relationships, and potential applications of each compound were studied as well [22]. Based on these works, a thorough search of both the ClinicalTrials.gov and the European Union Clinical Trials Register was conducted with a view to identifying completed and ongoing clinical studies investigating the role

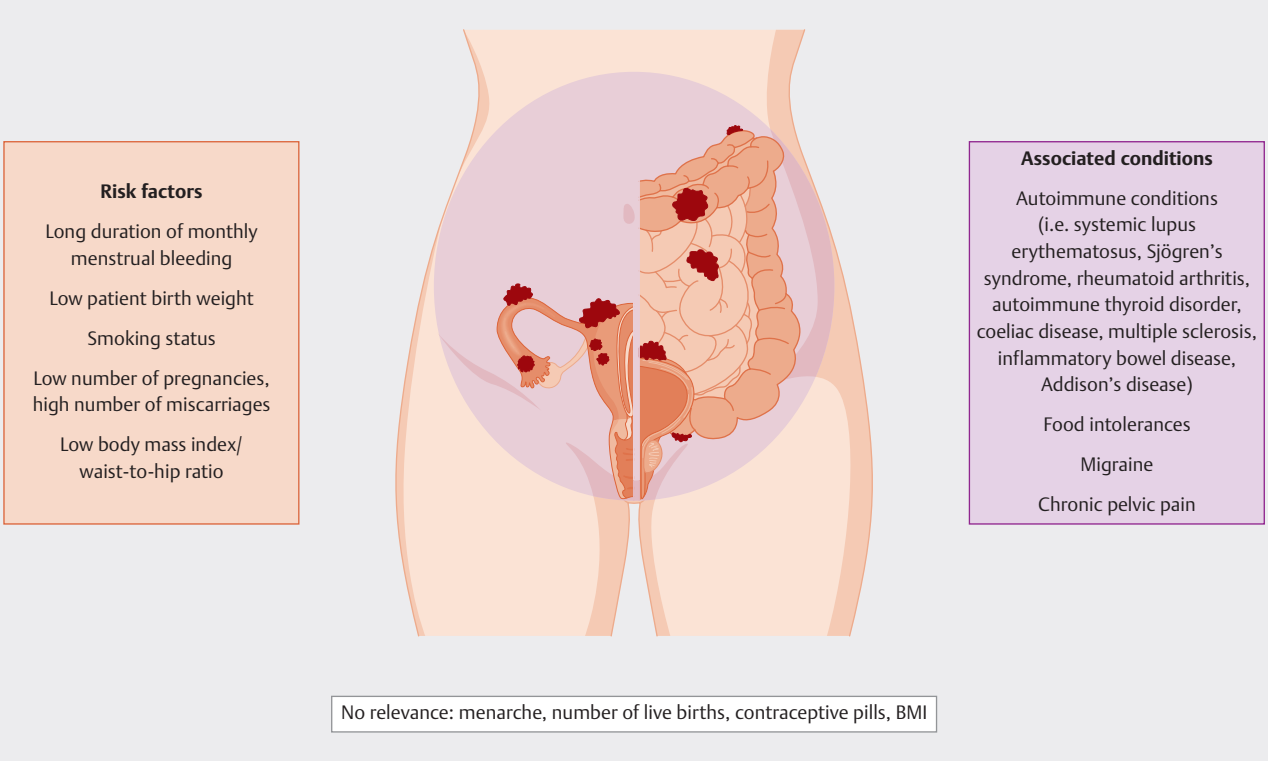
▶**Table 3** Preclinical studies on the role of signaling pathways in endometriosis.

Agent	Pathway	Preclinical study (cell culture/animal model/tissue sample)
Indomethacin	COX-2	Mice model
Celecoxib	COX-2/PGE2, COX-2/VEGF	Primary human endometriotic stromal cells
BAY11-7085	Caspase and apoptotic proteins effects	Primary human endometriotic and endometrial stromal cells
Chloroindazole	E2/ER	Primary human endometriotic stromal cells and mice model
Oxabicycloheptene sulfonate	E2/ER	Primary human endometriotic stromal cells and mice model
Tunicamycin	ER stress	Primary human endometriotic and endometrial stromal cells
Verteporfin	Hypoxia/LATS1/YAP1	Primary human endometriotic stromal cells and mice model
Curcumin	p53/NF-κB, IκKα/β, STAT3, and JNK	Mice model
Genistein	COX-2 and NF-κB/MMP-2/MMP-9	Mice model
Sorafenib	RAF/MEK/ERK and VEGF/VEGFR	Primary human endometriotic stromal cells and mice xenograft model
Vemurafenib	MAPK/ERK	Primary human stromal epithelial; endometriotic/endometrial cells and animals mice xenograft model
U0126	MAPK/PR	Primary human endometriotic and endometrial stromal cells
Puerarin	MAPK/ERK1/2	Primary human endometriotic stromal cells
PGE2 inhibitors	EGFR/ERK1/2, Akt, B-catenin, NF-κB	Cell line (12 Z and 22 B), primary human endometriotic and endometrial stromal cells
WIN 55212-2	mTOR/Akt	Primary human stromal/epithelial; endometriotic/endometrial cells and mice xenograft model
Propofol	p53, p21, Caspase, FOXO, inducing apoptosis	Cell line (CRL-7566)
Dichloroacetate	Metabolic process	Primary human peritoneal mesothelial cells, cell line (SHT290), mice model
MK2206 and chloroquine	Akt/PR, Autophagy modulators regulated autophagy	Primary human stromal/epithelial; endometriotic/endometrial cells and mice xenograft model
Ginsenoside	NF-κB, E2/ER and PR, NK cells cytotoxicity	Primary human endometriotic and endometrial stromal cells and mice model
Müllerian inhibiting substance	ERK and Beclin1 inducing autophagy, CDK	Cell line (CRL-7566)
C-82	CBP/β-catenin	Primary human endometriotic and endometrial stromal cells
ICG-001	CBP/β-catenin	Primary human endometriotic and endometrial stromal cells and mice model
Metformin	Wnt2/β-catenin, cytokines	Primary human endometriotic and endometrial stromal cells, endometrial epithelial cell
PKF115-584/ CGP049090	Wnt/β-catenin	Primary human stromal/epithelial; endometriotic/endometrial cells
Fasudil	Rho/ROCK	Primary human endometriotic stromal cells
Heparin	Rho/ROCK	Primary human endometriotic stromal cells
Pazopanib, sunitinib and sorafenib	VEGF/VEGFR	Rat model
Pyrrolidine dithiocarbamate	NF-κB/TNFα/VEGF	Primary human endometriotic and endometrial stromal cells
Pentoxifylline	VEGFC and VEGFR2	Wistar rat model
N-acetylcysteine	Radical scavenging activity/ERK, cytokines	Primary human stromal/epithelial; endometriotic/endometrial cells, mice xenograft model
Caffeic Acid	Regulation of antioxidant enzymes	Primary human endometriotic and endometrial stromal cells
Crocin	Cytokines	Mice model and cell lines (HUVEC and THP-1)
ISO-1	Cytokines	Mice model
Puerarin	E2/ER	Rat model

▶**Table 3** continued

Agent	Pathway	Preclinical study (cell culture/animal model/tissue sample)
Niclosamide	MAPK, Wnt pathway	Mice model
Acai	VEGF/VEGFR, iNOS/NO, COX-2/PGE2	Cell line (J774.G8) and Sprague-Dawley rats
Bortezomib	Proteasome	Wistar rats
TPCK	NF-κB	Endometriosis stromal cells
PDTC	IkappaB	Endometriosis stromal cells and Wistar rats
Thalidomide	IkappaB	Endometriosis stromal cells and Sprague-Dawley rats
Thiazolidinediones	PPARγ	Sprague-Dawley rats
Interleukin 10	DNA binding	Endometriosis stromal cells
Decoy Nucleotides	DNA binding	Endometriosis stromal cells
SB203 580	Interleukin 1β	Endometriosis stromal cells
SP600 125	JNK	Endometriosis stromal cells
Temsirolimus	mTOR	Endometriotic cells

Abbreviations: CBP = CREB binding protein; CDK = Cyclin dependent kinase; COX = Cyclooxygenase; CXCL3 = Chemokine (C-X-C motif) ligand 3; ER = Estrogen receptor; FOXO = Forkhead box transcription factors; GnRH = Gonadotropin-releasing hormone; IFN = Interferon; IκK = Inhibitor of kappa kinase; iNOS = Inducible-NO synthase; JNK = Jun N-terminal kinase; LATS1 = Large tumor suppressor kinase 1; LHRH = Luteinizing hormone-releasing hormone; MAPK = Mitogen-activated protein kinase; MMP = Matrix metallopeptidase; mTOR = Mammalian target of rapamycin; NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells; NK = Natural killer; NO = Nitric oxide; PDTC = Pyrrolidine dithiocarbamate; PGE = Prostaglandin; PPARγ = Peroxisome proliferator-activated receptor gamma; RAF/MEK/ERK = Rapidly accelerated fibrosarcoma/mitogen-activated protein kinase/extracellular signal-regulated kinase; ROCK = Rho-associated, coiled-coil containing kinases; SMAD = Suppressor of mothers against decapentaplegic; STAT3 = Signal transducer and activator of transcription 3; TGF = Transforming growth factor; TNFα = Tumor necrosis factor α; TPCK = Tosyl phenylalanyl chloromethyl ketone; VEGF = Vascular endothelial growth factor; WNT2 = Wnt family member 2; YAP1 = Yes-associated protein 1



▶ **Fig. 4** Risk factors and associated conditions with endometriosis [14, 17, 23, 24, 25, 26].

of the aforementioned pathways in patients with endometriosis. ▶ **Table 1** and ▶ **Table 2** briefly summarize the search results. ▶ **Table 3** provides a brief overview of the relevant preclinical studies.

Discussion and Conclusion

A great number of extensive review articles has so far been published on the role of signaling pathways/molecules in endometriosis [16, 17, 18, 19, 20, 21, 22]. Of note, given some shared molecular (genetic) mechanisms, endometriosis seems to be associated with various risk factors and other disease entities such as migraine, autoimmunity and chronic pelvic pain [23, 24, 25, 26] (▶ **Fig. 4**). Chronic pain, for instance, seems to share similar pathomechanisms as endometriosis in terms of abundance of pro-inflammatory molecules, angiogenesis and estrogen-dependent pain meditation [23]. Even though endometriosis is not yet officially classified as an autoimmune disease, there are a number of similarities between the two conditions, including a predominance of females (and hormones), immunological abnormalities, genetic polymorphisms, as well as chronicity [24]. In the case of migraine, mechanisms associated with sex hormone activities, protein adhesion, phosphorylation, inflammation or immune dysregulation seem to play a similar role as in the pathogenesis of endometriosis [25]. Endometriosis is a disease condition encountering gynecologists every single day in both the outpatient and the clinic routine. Patients seek medical advice either because of the adverse pain symptoms and/or due to the unfulfilled desire to become pregnant. Unfortunately, most patients are very disappointed once they learn that surgery does not grant the end of the disease and that the only possible symptomatic treatment is hormone-based. In times of targeted treatment therapies and ample possibilities to investigate and discover novel therapeutic approaches (i.e. inflammation, apoptosis, angiogenesis, cellular adhesion, etc.), endometriosis represents a profound example of an understudied disease that to date may only be treated symptomatically. The present work aims at raising the awareness of both researchers and clinicians in this context and to highlight the need of further research in order to establish and launch targeted therapies for the successful treatment of endometriosis patients. All in all, we herein intended to summarize the current research status and to point out the field's novel therapeutic approaches. However, the considerable side effects of these targeted therapies need to be further examined and taken into consideration in the context of risk–benefit calculation.

Contributors' Statement

Conceptualization, I.P., M.W.B.; literature research, original manuscript preparation, art work, I.P.; review and supervision, S.B., K.A., L.H., L.W., L.L. and M.W.B. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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