REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Endometriosis

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Endometriosis is defined as the presence of endometrium-like tissue outside the uterus.[1] However, this definition does not encompass the complex symptomatic, pathobiologic, and multisystemic nature of the disorder (Fig. 1).[2] Endometriosis is primarily diagnosed through surgical visualization — ideally, laparoscopy. Treatment consists of surgical removal of lesions and hormonal medication, often with side effects and variable efficacy. The 2008 U.S. health care costs for endometriosis were approximately $4,000 per affected woman, which is similar to the costs for other chronic conditions such as type 2 diabetes, Crohn's disease, and rheumatoid arthritis.[3] The costs of care to manage symptoms, including chronic pelvic pain, dysmenorrhea, deep dyspareunia, dysuria, dyschezia, fatigue, and infertility, are much greater, since these symptoms affect physical, mental, sexual, and social well-being, as well as productivity.[4-6]

Despite the substantial effect that endometriosis has on women, their families, and the economy, public and professional awareness of the disorder remains poor.[3,7] Here, we discuss the epidemiology, pathophysiology, and pathogenesis of endometriosis, as well as diagnosis and treatment, with an emphasis on how understanding the genetic origins of the disease can inform development of better diagnostic and treatment options.

EPIDEMIOLOGY

PREVALENCE

Endometriosis is estimated to affect 10% of reproductive-age women,[8] which extrapolates to approximately 190 million women worldwide, given the World Bank's population estimates for 2017.[9] The true prevalence of endometriosis is uncertain, however, because definitive diagnosis requires surgical visualization. Estimates vary widely among population samples and diagnostic approaches.[10] The prevalence ranges from 2 to 11% among asymptomatic women, 5 to 50% among infertile women, and 5 to 21% among women hospitalized for pelvic pain.[8] Among symptomatic adolescents, the prevalence of endometriosis ranges from 49% for those with chronic pelvic pain to 75% for those with pain that is unresponsive to medical treatment.[8]

Knowledge of population distributions, disease manifestations, and risk factors is limited to data for women in whom endometriosis is successfully diagnosed. The number and characteristics of undiagnosed cases are unknown. Once we have more definitive epidemiologic and clinical data (perhaps through the use of future, noninvasive diagnostics), we may learn that everything we currently believe about endometriosis, which is biased toward factors associated with access to care, may represent only a portion of the story.[8]

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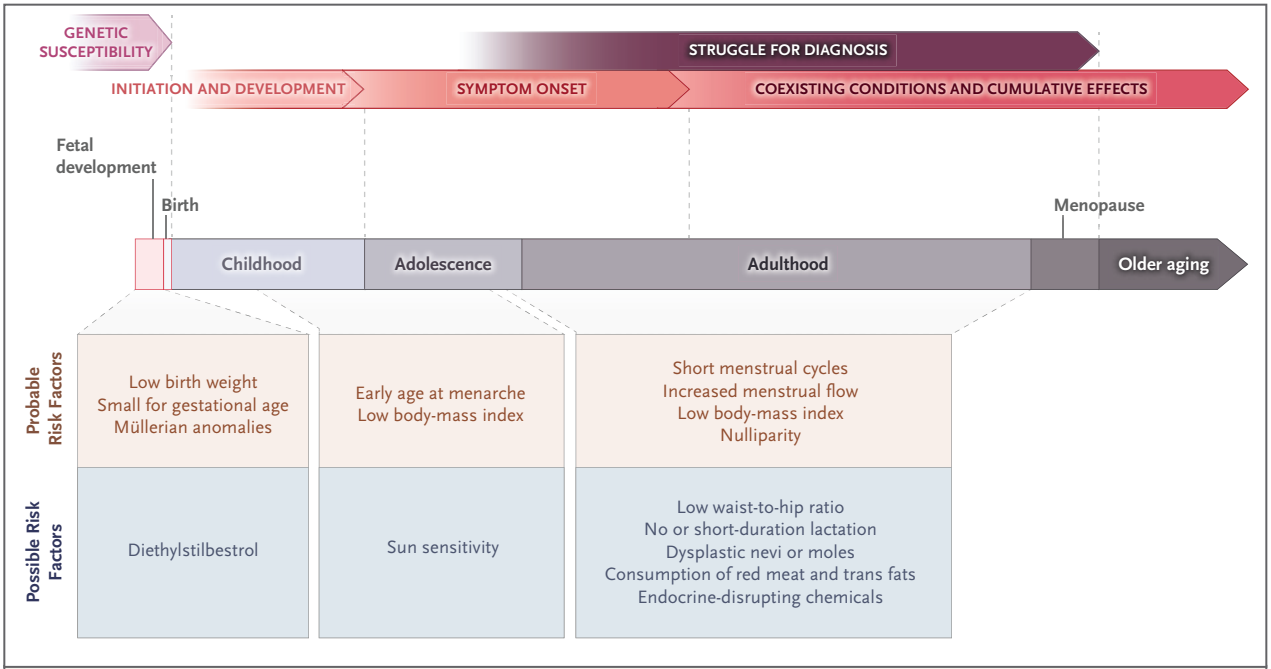


Figure 1. Endometriosis across the Life Course.

Although the natural history of endometriosis remains unknown, emerging evidence suggests that there are critical windows of exposures and development. Since the onset of endometriosis-associated pain symptoms is most often reported during adolescence and young adulthood, the pathophysiological steps of initiation and development of endometriosis must occur earlier in the life span. Genetic loci have been associated with a risk of endometriosis; there is also evidence of life stage–specific risk factors. Before a definitive diagnosis is made, women often endure symptoms for years while negative effects on well-being and quality of life, in addition to multisystemic coexisting conditions, accumulate.

PRESENTATION, RISK FACTORS, AND COEXISTING CONDITIONS

Presentations of endometriosis (Fig. 2) range from superficial peritoneal lesions of varying color, to cysts in the ovaries (endometrioma), to nodules with a depth of penetration exceeding 5 mm (deep endometriosis, often accompanied by scarring [fibrosis] and adhesions[1]), to extrapelvic lesions (Fig. 3). More severe endometriosis, according to the widely used, revised American Society of Reproductive Medicine (rASRM) staging classification (stages I through IV; see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), does not correlate with symptoms, treatment response, or prognosis.[11] Although the natural history of endometriosis is unknown, subphenotypes of lesions may vary across the life course.[1,12] However, no robust evidence supports an ordered progression of endometriotic lesions. In studies of repeat surgeries, lesions progressed (in 29% of cases), regressed (in 42%), or were static (in 29%), according to rASRM staging[13]; symptom severity or recurrence was not correlated with stage. Since classification and staging systems have failed to provide informative clinical algorithms for determining risk or prognosis,[14] some people have argued that a definition of the symptomatology should include probable endometriosis.[10,15]

Symptom heterogeneity is high (Fig. 2). Women with rASRM stage I disease (defined as a limited number of lesions and few adhesions) may have severe pain, infertility, or both, whereas women with stage IV endometriosis (a greater number of lesions, endometrioma, or both, with extensive adhesions; see Table S1) may be asymptomatic.[14] Pelvic pain may be inflammatory as well as neuropathic in nature,[16] characterized by potential sensitization of the central nervous system that can result in persistent pain even after endometriotic lesions have been excised.[17,18] Chronic pelvic pain that is unresponsive to conventional treatments develops in approximately

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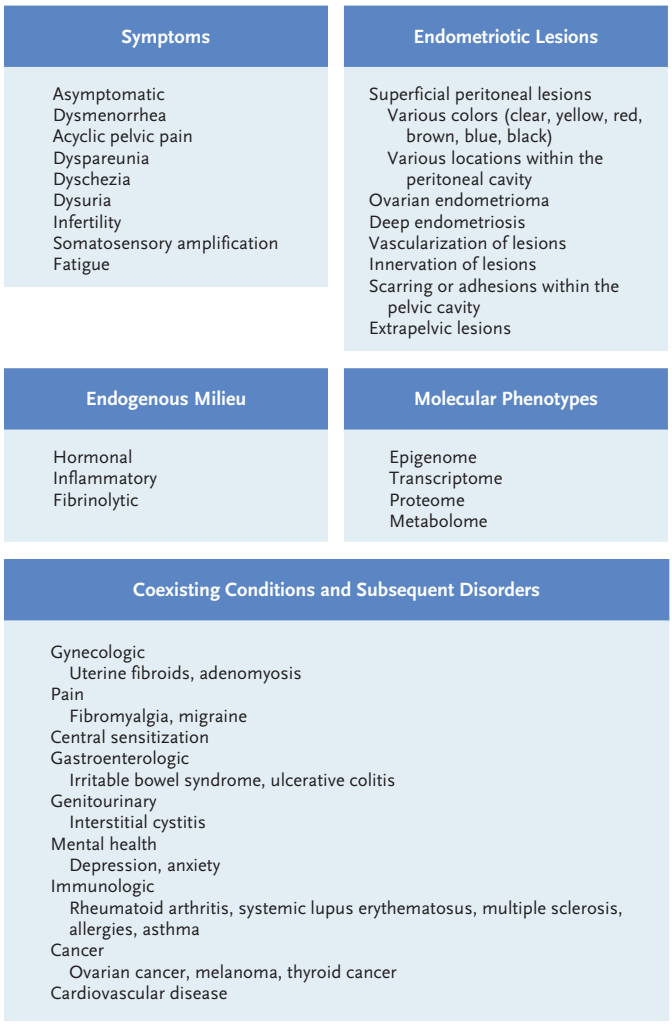


Figure 2. Multisystemic Endometriosis Phenome.

The presentation of endometriosis is complex and heterogeneous. Symptomatically, it includes several hallmark yet nonspecific types of pain and an increased risk of infertility, as well as prevalent fatigue. The gross appearance of endometriotic lesions suggests multiple subtypes. Altered aspects of the endogenous milieu include local estrogen production and progesterone resistance, as well as chronic local and systemic inflammation. Recognition of varied molecular phenotypes among women with endometriosis is emerging; such phenotypes may prove to be correlated with the presence of myriad coexisting conditions and subsequent disorders that span multiple organ systems.

30% of patients with endometriosis.[19] About one third of affected women have infertility (approximately twice the rate among women without endometriosis).[20]

The few robust risk-factor associations that are emerging suggest critical windows of exposure (Fig. 1).[8] For example, diethylstilbestrol exposure, low birth weight, and an early age at menarche have been associated with a greater risk of endometriosis. Risk factors from adolescence into adulthood include a short menstrual cycle, low body-mass index, low waist-to-hip ratio, and low parity.[8] Whether these associations represent causes or consequences of endometriosis must be interpreted cautiously, given our rudimentary knowledge of the initiation and development of the disorder and our inability to diagnose it before the onset of symptoms.

Women with endometriosis are more likely than women without endometriosis to have coexisting conditions[8,21] (Fig. 2). A robust association has been shown between endometriosis and the risk of clear-cell and endometrioid ovarian cancer (meta-analytic odds ratio, 1.42).[22] This finding currently has little clinical significance in terms of the absolute lifetime risk of ovarian cancer (1.8% among women with endometriosis vs. 1.3% in the general population of women), but a better understanding might lead to the identification of subphenotypes of endometriosis that are associated with the highest risk of ovarian cancer. Increased risks of melanoma, non-Hodgkin's lymphoma, and thyroid and endometrial cancers has been observed but with less consistent evidence.[21]

Coexisting gynecologic conditions such as adenomyosis and uterine fibroids, as well as associations with endometrial cancer, can be influenced by diagnostic biases and failure to distinguish between diagnoses in women undergoing hysterectomy and those in women with intact uteri.[1,8,10] In addition, a meta-analysis showed an increased risk of several autoimmune diseases among women with endometriosis, but most of the studies were of insufficient quality.[23] Future studies of coexisting conditions should assess the timing of the onset of the condition (relative to a woman's history of endometriosis), diagnostic bias, and potential confounding factors such as correlated risk factors and physiological features and should explore endometriosis treatments as mediators of these associations.

PATHOGENESIS AND PATHOPHYSIOLOGY

The development of endometriosis involves interacting endocrine, immunologic, proinflammatory, and proangiogenic processes (Fig. 4),

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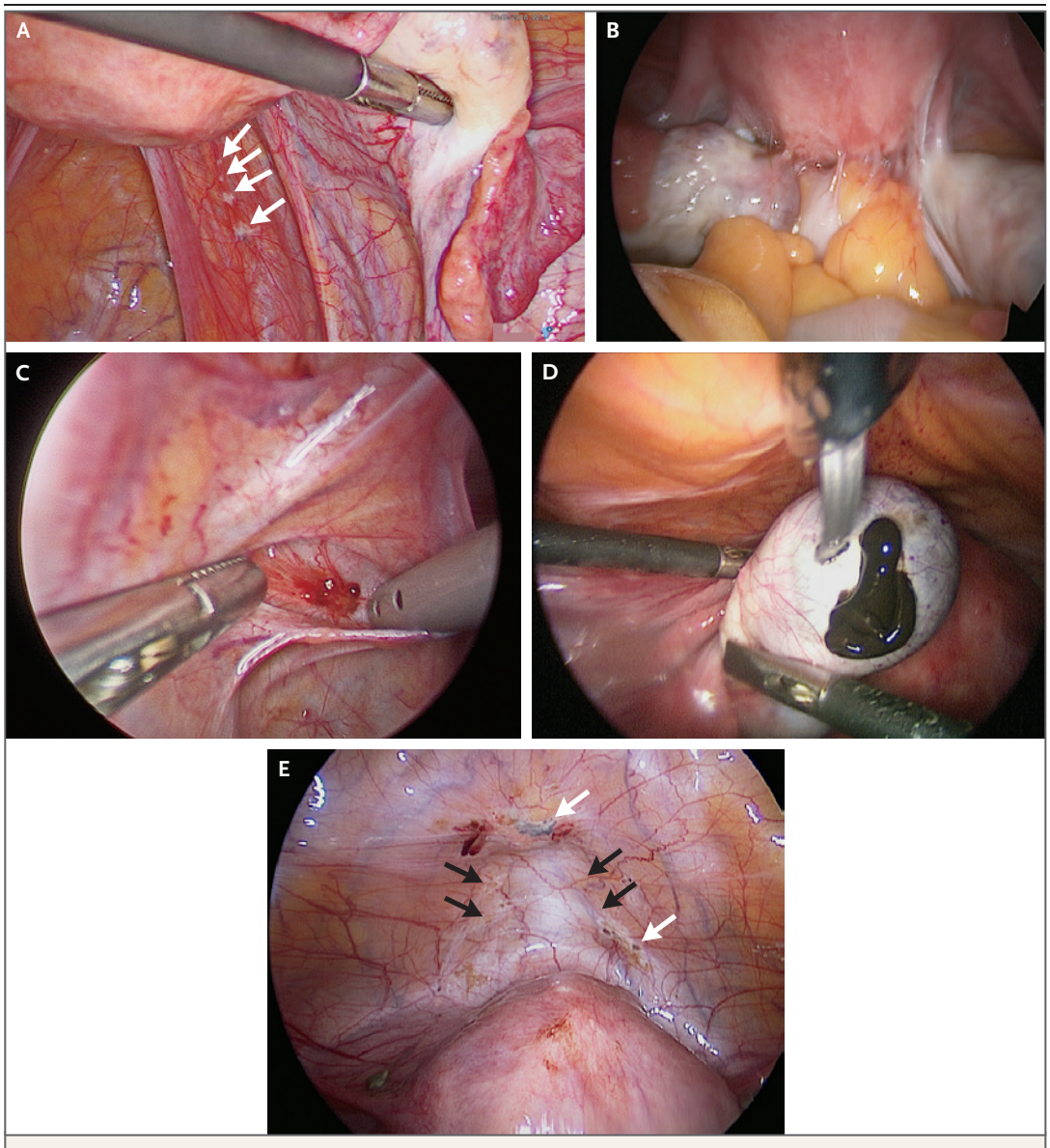


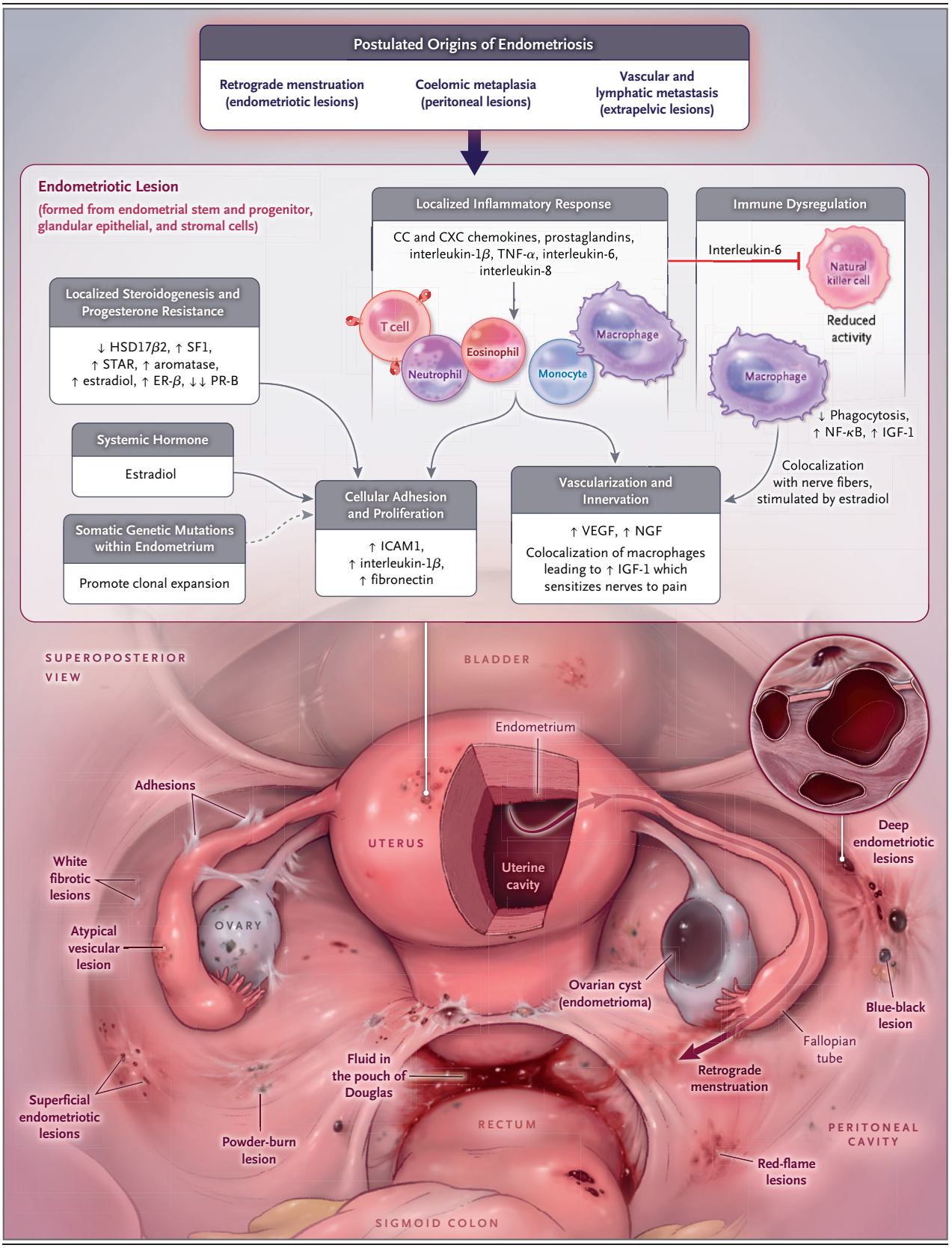
Figure 3. Multiple Manifestations of Endometriosis.

Panel A shows minimal endometriosis with four peritoneal endometriotic lesions (white arrows) on the right pelvic side wall. Panel B shows extensive endometriosis with bowel adhesions to the uterus and obliteration of the posterior cul-de-sac. Panel C shows a superficial red peritoneal endometriotic lesion and hyperemia. Panel D shows an endometrioma ("chocolate cyst") in the left ovary. Panel E shows a deep bladder nodule (black arrows) and red, brown, and black peritoneal endometriotic lesions (white arrows).

which have been detailed recently elsewhere.[1] Whether these factors are pathogenic (causal) or merely represent a feature of the pathophysiological process typically measured years after symptom onset remains uncertain.

The postulated origins of endometriotic tissue are retrograde menstruation, coelomic metaplasia, and lymphatic and vascular metastasis. Retrograde menstruation refers to the reflux of menstrual debris containing viable endometrial cells through the fallopian tubes into the peritoneal cavity.[24] Retrograde menstruation as an origin of endometriosis is supported by studies showing risk associations with a short menstrual cycle and obstructed menstrual flow,[1,8] as well as by cellular studies tracing the origins of

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Figure 4 (facing page). Potential Pathways for the Pathogenesis and Pathophysiological Features of Pelvic Endometriosis.

The pathogenesis and pathophysiological features of pelvic endometriosis are complex. Potential origins of the endometriotic lesions include transplantation of endometrial tissue through retrograde menstruation and in situ coelomic metaplasia of the peritoneal lining. Vascular or lymphatic metastasis most likely occurs only rarely, in cases of extrapelvic lesions. Superficial and deep endometriotic lesions are established and maintained through interacting molecular mechanisms that promote cellular adhesion and proliferation, systemic and localized steroidogenesis, localized inflammatory response and immune dysregulation, and vascularization and innervation. The dashed arrow indicates a postulated effect. ER denotes estrogen receptor, HSD17β2 17β-hydroxysteroid dehydrogenase 2, ICAM intercellular adhesion molecule, IGF insulin-like growth factor, NF-κB nuclear factor κB, NGF nerve growth factor, PR progesterone receptor, SF1 steroidogenic factor, STAR steroidogenic acute regulatory protein, TNF tumor necrosis factor, and VEGF vascular endothelial growth factor.

somatic genetic mutations observed in endometriotic lesions to eutopic endometrium.[25] Neonatal uterine bleeding, containing endometrial stem cells, could explain rare premenarchal endometriosis.[26] Coelomic metaplasia — the transformation of peritoneal mesothelium into glandular endometrium — has been suggested in women with müllerian duct defects.[27] Lymphatic and vascular metastasis — the transport of endometrial cells through lymphatic and blood vessels — has been proposed as another origin of extrapelvic endometriosis.[28]

Since retrograde menstruation is common,[29] other factors must determine the ability of endometrial cells to adhere to peritoneal surfaces, proliferate, and develop into endometriotic lesions (Fig. 4).[30] Endometrial stem-cell and progenitor-cell populations are present in eutopic endometrium,[31] which, if shed in retrograde menstruation, may play a role in the development of endometriotic lesions. Endometrial stromal cells from women with endometriosis display adhesive capacity as a result of altered integrin profiles,[32] and a localized inflammatory response in endometriosis favors cellular adhesion.[33]

Proliferation of endometriotic deposits requires estradiol, which is provided by systemic hormones and also locally from increased expression of aromatase and steroidogenic acute regulatory protein and decreased expression of 17β-hydroxysteroid dehydrogenase 2 by endometriotic lesions.[34] In addition, lesions are characterized by increased expression of estrogen receptor β,[35] which has been shown in a mouse model to promote lesion growth by inhibiting tumor necrosis factor α (TNF-α)–induced apoptosis, increasing interleukin-1β levels, enhancing cellular adhesion and proliferation, and increasing the epithelial–mesenchymal transition.[30] Furthermore, suppression of progesterone receptor B in eutopic and ectopic endometrium, enhanced in ectopic endometrial stromal cells by epigenetic differential methylation of *PR-B*, *HOX*, and *GATA* family transcription-factor genes,[36] results in disturbed progesterone signaling ("progesterone resistance"),[37] inhibiting estrogen-dependent epithelial-cell growth and dysregulating endometrial decidualization, the process by which the endometrial lining prepares for pregnancy.[1,38]

Endometriotic cells and tissue elicit a localized immune and inflammatory response with the production of cytokines, chemokines, and prostaglandins. Dysfunction of the innate and adaptive immune system[33] is evident,[23] but it is unclear whether immune dysfunction initiates endometriosis or is a pathophysiological hallmark of the disorder. A study of inflammatory markers collected years before the diagnosis of endometriosis showed a greater risk with higher plasma interleukin-1β levels.[39]

The inflammatory response involves monocytes and macrophages, neutrophils, T cells, and eosinophils attracted by CC and CXC chemokines produced in ectopic endometrium (Fig. 4).[40] In the innate immune system, the neutrophil response is mediated by the expression of the CXC chemokine interleukin-8 and CCL2 (monocyte-chemoattracting protein 1) by endometriotic stromal cells.[33] Monocytes, eosinophils, and T cells are attracted by the production of CCL5 (RANTES) and CCL2 in both ectopic lesions and peritoneal fluid from women with endometriosis.[40] Local natural-killer-cell activity is impaired in women with endometriosis, which may contribute to immune evasion of endometrial cells.[41] Macrophages in peritoneal fluid are characterized by decreased phagocytic capacity and increased activation of proinflammatory cytokines (TNF-α, interleukin-1β, and interleukin-6) and proangiogenic factors (vascular endothelial growth factor), as well as growth factors and adhesion molecules.[1,33] Cytokine production is further

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enhanced by overexpression of nuclear factor κB by peritoneal macrophages and endometriotic stromal cells, production of reactive oxygen species, and activation of mitogen-associated kinase (MAPK) signaling pathways.[42] The contribution of the adaptive immune system to endometriosis that involves T-cell and B-cell responses is less well characterized. Type 17 helper T-cell concentrations are increased in peritoneal fluid from women with endometriosis, resulting in increased interleukin-17 expression and promoting chronic inflammation.[33]

The complex endocrine and proinflammatory microenvironment in and surrounding endometriotic lesions promotes their proliferation and vascularization but also nociception.[43] The endometrium and endometriotic lesions contain nerve fibers[17] stimulated by inflammatory mediators. Macrophages colocalize with nerve fibers, promoted by locally synthesized estradiol,[44] and produce nerve-sensitizing insulin-like growth factor 1.[45] The ascending nociceptive signals received in the central nervous system can lead to heightened responsiveness of nociceptive neurons to normal or subthreshold afferent input (central sensitization)[17] and alterations in pain processing.

As with other chronic pain conditions, pain mechanisms in endometriosis extend beyond the presence of endometriotic lesions alone. Pelvic pain in women with endometriosis, featuring enhanced anterior insula glutamatergic neurotransmission and connectivity with the medial prefrontal cortex, is associated with changes in brain chemistry and function, as compared with brain chemistry and function in age-matched, pain-free women.[18] Women with endometriosis are also at high risk for cross-organ sensitization (pain perception from adjacent structures due to convergence of neural pathways), which may explain poor postsurgical pain relief in many affected women.[16] The similarity of mechanisms underlying different pain conditions is an important area of research for cross-disciplinary identification of drug targets and prevention of chronic pain.

GENETIC FEATURES

Genetic studies of endometriosis have focused on uncovering heritable (germline) genetic variation and, more recently, tissue-based somatic (cellular acquired) genetic variation to improve our understanding of the disease.

HERITABLE FEATURES

Twin studies have estimated the heritability of endometriosis (the proportion of disease risk attributable to genetic variation) at approximately 50%.[46] Whole-genome linkage studies involving families with multiple cases of endometriosis identified two linkage regions, probably harboring rare risk variants[47] that remain unidentified. Signal strengths indicated that these findings are unlikely to explain a large proportion of familial endometriosis risk, in contrast to, for example, *BRCA1* and *BRCA2* variants in breast cancer.[48]

Common genetic variation accounts for approximately 26% of the risk of endometriosis[49]; common risk variants are detectable in sufficiently powered, population-based genomewide association studies.[50] Ten genomewide association studies of endometriosis, limited to women of European and Japanese ancestry, identified 18 genomewide significant loci, 14 of which were robustly replicated (Table S2).[1,51] A meta-analysis involving 25 global data sets is ongoing, with interim results[52] pointing to 27 genomewide significant loci (13 of which are novel) that account for 2.2% of disease variance for endometriosis and 3.8% for rASRM stage III or IV disease. Genetic correlations with coexisting chronic pain conditions (headache and back and joint pain) suggest a genetic basis for susceptibility to pain in women with endometriosis.

Larger samples increase the number of loci observed in genomewide association studies,[50] but transethnic studies, including non-European ancestries, are needed for endometriosis. A key challenge is to understand how genomewide significant loci contribute to the pathogenesis of endometriosis. Analysis of genes nearest to the loci implicate pathways previously postulated to be involved (Fig. 4): cell adhesion and proliferation, angiogenesis, inflammation, and hormonal pathways.[51] Furthermore, MAPK signaling has been implicated as a pathway involved in rASRM stages I and II of endometriosis, possibly related to pain processing, signal transducer and activator of transcription 3 (STAT3) signaling shared with endometrial cancer, and WNT signaling shared with fat distribution.[1] However, the location of a variant in or near a specific gene does

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not imply that the transcription of this gene is affected. An example for endometriosis is variant rs3820282 in an intron of *WNT4*, which studies showed was correlated with expression of *CDC42* and *LINC00339* but not *WNT4*.[53]

Functional elucidation of variants implicated by genomewide association studies in the pathogenesis of endometriosis requires integrated analyses of genomic data with epigenomic, transcriptomic, metabolomic, and proteomic data in tissues and cell types relevant to the disorder (Fig. 2). Such information is currently absent from public resources such as the National Institutes of Health Epigenome Roadmap, Genotype-Tissue Expression (GTEx), and the Encyclopedia of DNA Elements (ENCODE). In addition, integration with deep phenotypic clinical data is required to aid phenotypic characterization of molecularly defined subtypes. These investigations will lay the groundwork for developing subphenotype-specific approaches to precision medicine. The Endometriosis Phenome and Biobanking Harmonisation Project of the World Endometriosis Research Foundation has provided tools for standardized data and sample collection in studies of endometriosis.[54]

SOMATIC FEATURES

The association between endometriosis and clear-cell or endometrioid ovarian cancer[22] has led to an interest in the role of somatic mutations in genes implicated in ovarian cancer — in particular, *PIK3CA* and *ARID1A*.[55] An analysis of the exomes of 24 deep endometriosis nodules, as compared with adjacent normal peritoneum, showed somatic cancer driver mutations in endometriotic tissue from 5 of 24 patients (21%) for *ARID1A*, *KRAS*, *PIK3CA*, and *PPP2R1A*, with mutations confined to glandular epithelial cells.[56] Exome and targeted sequencing analysis of epithelium dissected from 107 endometrioma samples, as compared with 82 histologically normal, eutopic endometrium samples, identified cancer-associated hot-spot mutation sites in *KRAS* and *PIK3CA* in both endometriotic and endometrial epithelium.[25] The allele frequency of observed driver mutations suggested clonal expansion of epithelial cells carrying these mutations, transported through retrograde menstruation. However, the presence of hot-spot mutations in *KRAS*, *PIK3CA*, and *FGFR2* in more than 50% of 110 histologically normal endometrial samples from women without evidence of gynecologic disease[57] casts doubt on the association of such mutations with cancer risk or on their usefulness for diagnostic screening.

RISK PREDICTION BASED ON GENETIC VARIANTS

Progress in unraveling genomics for endometriosis lags far behind that for other common diseases. For example, 243 loci identified in genomewide association studies are now known for type 2 diabetes and 172 for breast cancer, explaining approximately 18% of disease variance.[58,59] Robust polygenic risk scores generated for these conditions have discriminatory potential to identify high-risk persons that approaches the discriminatory potential of highly penetrant monogenic mutations.[60] The ongoing WISDOM (Women Informed to Screen Depending on Measures of Risk) trial aims to use polygenic risk scores, along with other factors, to assign women to breast-cancer screening regimens that are tailored to their risk profile.[61] Such risk prediction is not currently feasible for endometriosis, since variants identified in genomewide association studies to date explain only a small percentage of risk.

DIAGNOSIS

Endometriosis remains difficult to diagnose. No biomarkers to detect or rule out endometriosis are available.[62] The predominantly intraabdominal location of the lesions, plus their small size, means that laparoscopic visualization (ideally with histologic verification) remains the standard for diagnosis of the disease.[63] Imaging is of little use for identifying the most prevalent of the three macropresentations described above: superficial peritoneal lesions.[64] However, endometriomas can be identified reliably by transvaginal ultrasonography or magnetic resonance imaging (MRI), with more than 90% sensitivity and specificity.[64] A skilled specialist can identify deep endometriosis and adhesions involving pelvic organs with transvaginal ultrasonography. MRI has 94% sensitivity for detecting deep endometriosis, but the specificity is only 79%.[64]

Although most adults report that their pelvic pain began during adolescence,[5] most young women do not receive timely treatment. Women see, on average, seven physicians before endometriosis is diagnosed.[5,65] The varied symptom-

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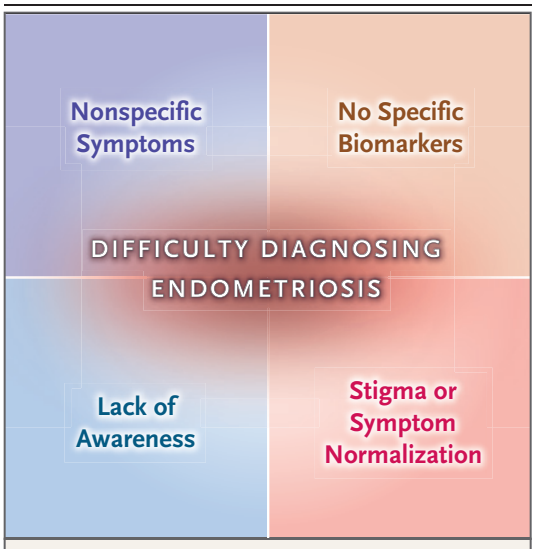


Figure 5. The Diagnostic Challenge in Endometriosis.
The diagnostic challenge in endometriosis is multifaceted. Symptoms such as dysmenorrhea, dyspareunia, dyschezia, and infertility can be attributed to many conditions. In addition, these symptoms are often not discussed openly because of the fear of stigmatization. Furthermore, awareness of the disease is poor on the part of the general public, employers, and persons in health care professions. Finally, no clinically relevant biomarkers are available. As a result of all these factors, the average delay between the onset of symptoms and diagnosis is 7 years.

atology can also be attributed to other conditions,[66] and symptom-based algorithms are inadequately predictive.[67] Women often undergo clinical examinations or imaging with low sensitivity for peritoneal endometriosis.[10] Surgery is appropriate only when symptoms reach a level of severity to justify the risk. However, the threshold for surgical referral varies not only according to the practitioner's awareness of endometriosis and associated pelvic pain but also with economic and geographic access to care. Specialists in endometriosis are in short supply, and women in large regions of the world, including the United States, live long distances from the nearest appropriately skilled practitioner. The long interval between symptom onset and diagnosis results in prolonged pain, decreased quality of life, psychological stress, and impaired fecundity.[5] The complex diagnostic challenge of endometriosis — a tetrad (Fig. 5) of nonspecific symptoms, lack of sensitive and specific biomarkers, and lack of awareness on the part of both the public (with symptoms discounted) and practitioners (with symptoms dismissed or inadequately investigated) — drives the delay in diagnosis.[5,10]

TREATMENT

In choosing treatment for endometriosis, it is crucial to consider the patient's predominant symptoms and preferences, side-effect profile, and age, as well as the extent and location of disease, previous treatment, and costs. Management of endometriosis (particularly disease involving the bowel, bladder, ureters, or extrapelvic structures and cases with overlapping pain conditions) requires multidisciplinary expertise.[14,16] Approximately 50% of women with endometriosis have recurrent symptoms over a period of 5 years, irrespective of the treatment approach.[68]

MEDICAL TREATMENT

Current hormonal treatment for endometriosis-associated pain focuses on systemic or local estrogen suppression, inhibition of tissue proliferation and inflammation, or both (Table S3). The oral contraceptive pill, both combined or progestin only, is widely used as the first-line treatment for dysmenorrhea or chronic pelvic pain with or without presumed endometriosis, particularly in primary care.[10] Daily or depot progestins have been effective in some women.[69]

Gonadotropin-releasing hormone (GnRH) agonists are second-line treatments that substantially suppress systemic estrogen levels. Menopause-like side effects, including bone loss, can be decreased by adding low-dose estrogen-replacement therapy.[63] Elagolix, the first GnRH antagonist for the treatment of endometriosis-associated pelvic pain, is now available in North America.[70] Oral administration of elagolix may allow for individualized dose adjustment, and early data indicate a dose-dependent effect on bone mineral density that is similar to the effect of other GnRH agonists (e.g., leuprolide, nafarelin, and goserelin).[70] Other oral GnRH antagonists (linzagolix and relugolix) are currently being evaluated in phase 3 clinical trials.

Localized aromatase production and resulting estradiol formation by endometriotic lesions[34] have prompted the successful off-label use of aromatase inhibitors for women with symptoms that are resistant to hormone therapy.[71] However, long-term use is restricted because of bone-density loss, vasomotor regulatory side effects

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such as flushing and hot flashes, and increased multiple-pregnancy rates.

Analgesia for endometriosis-associated pain consists of a combination of acetaminophen and nonsteroidal antiinflammatory drugs. The International Association for the Study of Pain recommends opioids for severe, short-lived pain during acute events but not for chronic pain conditions,[72] stating, "Chronic pain treatment strategies that focus on improving the quality of life, especially those integrating behavioral and physical treatments, are preferred."

COMPLEMENTARY TREATMENT

Pain physiology is a dynamic process affected by a complex interaction between amplifying and inhibitory neuronal networks and the result of accumulated peripheral signals from pelvic and extrapelvic organs. Pain is also affected by emotional, hormonal, and other physical and environmental influences. Thus, women with chronic pelvic pain should receive care from a multidisciplinary team consisting of a pain specialist, physical therapist, and psychologist, in addition to the gynecologist. Current therapeutic options range from pharmacologic treatment, including analgesic, anxiolytic, and antidepressant agents and membrane stabilizers, to pelvic physical therapy and cognitive behavioral therapy.[16]

SURGICAL TREATMENT

In women with hormone-resistant pain associated with endometriosis, surgical treatment should be considered. Surgery has been shown to decrease pain in some but not all women.[63] The aim is complete destruction or removal of endometriotic tissue and adhesions, and success in achieving this aim may largely depend on the skill of the surgeon. However, the evidence supporting surgical treatment of superficial endometriosis for pain relief is sparse and currently under debate.[73] Hysterectomy is common; endometriosis-associated pain is the leading indication for hysterectomy among women 30 to 34 years of age, accounting for 18% of all hysterectomies in the United States.[74] However, posthysterectomy pain is three times as likely among women with preoperative pain as among those without preoperative pain,[75] and about half of the 60% elevated risk of cardiovascular disease among women with endometriosis is attributed to the high rate of surgical menopause among such women.[8]

Excision of endometriomas adversely affects ovarian follicular reserve (as indicated by lower levels of anti-müllerian hormone and reduced antral follicle counts).[76] For women who want to preserve their fertility, the potential benefits of surgery should be weighed against these negative effects.[63] Although surgical treatment of endometriosis in women without other identifiable infertility factors may improve rates of spontaneous pregnancy, whether surgery improves the likelihood of pregnancy with assisted reproductive technology or in vitro fertilization remains unclear.[63,76]

THERAPEUTIC PROSPECTS

Current surgical and medical approaches to endometriosis are ineffective for a sizable proportion of women, and when effective, they can be associated with complications and morbidity. In addition, hormonal treatments are contraindicated for women with endometriosis who would like to conceive. Thus, nonhormonal therapeutic approaches that target the subphenotype of endometriosis are required for improved patient-centered outcomes. Currently, 15 registered clinical trials are focused on nonhormonal treatments (Table S4). An improved understanding of the pathogenesis of endometriosis and identification of precise macrolevel and molecular subphenotypes is needed for the development of targeted medical approaches.

Furthermore, an improved understanding of cross-organ and central sensitization in endometriosis, as well as clinical differentiation among pain characteristics, will lead management away from a mainly lesion-based approach and provide a wider spectrum of therapeutic targets. Inhibition of targeted pain receptors, such as the vanilloid receptor subtypes (transient receptor potential vanilloid [TRPV]) and *N*-methyl-D-aspartate (NMDA) glutamate receptors, and activation of cannabinoid receptors (CB1R and CB2R) are novel approaches that are currently being explored.[16] Nonpharmaceutical options, including acupuncture and local use of botulinum toxin, may ameliorate the musculoskeletal component of pelvic pain. Changes in diet may affect symptoms through antiinflammatory effects[8] and a contribution to a more favorable gut microbiome.[77] Finally, exploration of overlapping pain and mental health conditions may yield more precise individualized treatment.[16] Ulti-

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mately, the benefits and safety of new treatments must be proven in clinical trials with evidence-based core outcomes, including validated measures of pain assessment and remediation.[78]

No routine or standardized documentation has been developed for the presentation of endometriotic lesions or associated symptoms; detailed information is often absent from claims data and electronic medical records. Advances in the management of endometriosis, including identification of subphenotypes, development of diagnostic algorithms, and individualized treatment selection to improve prognosis and maximize symptom control, depend on the standardization of detailed phenotypic data and biologic-sample collection. The Endometriosis Phenome and Biobanking Harmonisation Project of the World Endometriosis Research Foundation offers tools for standardization.[54]

GOALS

Given the high prevalence of endometriosis, the cumulative effect of the disease on health and well-being across the life course, and the high associated economic costs, improvements in awareness, education, and action are long overdue. Stratified and individualized therapeutic approaches that maximize effective treatment and potentiate cure, as well as preventive measures, require definitive categorization of clinically informative endometriosis subphenotypes. Biomarkers are urgently needed, as are new therapeutics that target the varied physiological pathways related to the development and progression of endometriosis and the persistence of symptoms. Progress can be achieved only through sufficiently powered, collaborative, multidisciplinary research, facilitated by funding bodies by means of the prioritization of endometriosis as an important public health issue.

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REFERENCES

1. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. Nat Rev Dis Primers 2018;4:9.
2. Knapp VJ. How old is endometriosis? Late 17th- and 18th-century European descriptions of the disease. Fertil Steril 1999;72:10-4.
3. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod 2012;27:1292-9.
4. Gallagher JS, DiVasta AD, Vitonis AF, Sarda V, Laufer MR, Missmer SA. The impact of endometriosis on quality of life in adolescents. J Adolesc Health 2018;63:766-72.
5. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96(2):366.e8-373.e8.
6. Rush G, Misajon R, Hunter JA, Gardner J, O'Brien KS. The relationship between endometriosis-related pelvic pain and symptom frequency, and subjective wellbeing. Health Qual Life Outcomes 2019;17:123.
7. Shah DK, Moravek MB, Vahratian A, Dalton VK, Lebovic DI. Public perceptions of endometriosis: perspectives from both genders. Acta Obstet Gynecol Scand 2010;89:646-50.
8. Shafrir AL, Farland LV, Shah DK, et al. Risk for and consequences of endometriosis: a critical epidemiologic review. Best Pract Res Clin Obstet Gynaecol 2018;51:1-15.
9. The World Bank. Population ages 15-64 (% of population). 2017 (https://data.worldbank.org/indicator/SP.POP.1564.TO.ZS).
10. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. Am J Obstet Gynecol 2019;220(4):354.e1-354.e12.
11. Schliep KC, Mumford SL, Peterson CM, et al. Pain typology and incident endometriosis. Hum Reprod 2015;30:2427-38.
12. Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. J Pediatr Adolesc Gynecol 1997;10:199-202.
13. Hans Evers JLH. Is adolescent endometriosis a progressive disease that needs to be diagnosed and treated? Hum Reprod 2013;28:2023.
14. Johnson NP, Hummelshoj L, Adamson GD, et al. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod 2017;32:315-24.
15. Holt VL, Weiss NS. Recommendations for the design of epidemiologic studies of endometriosis. Epidemiology 2000;11:654-9.
16. Carey ET, Till SR, As-Sanie S. Pharmacological management of chronic pelvic pain in women. Drugs 2017;77:285-301.
17. Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. Science 2005;308:1587-9.
18. As-Sanie S, Kim J, Schmidt-Wilcke T, et al. Functional connectivity is associated with altered brain chemistry in women with endometriosis-associated chronic pelvic pain. J Pain 2016;17:1-13.
19. Caumo W, Deitos A, Carvalho S, et al. Motor cortex excitability and BDNF levels in chronic musculoskeletal pain according to structural pathology. Front Hum Neurosci 2016;10:357.

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20. Prescott J, Farland LV, Tobias DK, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod 2016;31:1475-82.
21. Kvaskoff M, Mu F, Terry KL, et al. Endometriosis: a high-risk population for major chronic diseases? Hum Reprod Update 2015;21:500-16.
22. Wang C, Liang Z, Liu X, Zhang Q, Li S. The association between endometriosis, tubal ligation, hysterectomy and epithelial ovarian cancer: meta-analyses. Int J Environ Res Public Health 2016;13(11):E1138.
23. Shigesi N, Kvaskoff M, Kirtley S, et al. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. Hum Reprod Update 2019;25:486-503.
24. Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol 1927;14:422-69.
25. Suda K, Nakaoka H, Yoshihara K, et al. Clonal expansion and diversification of cancer-associated mutations in endometriosis and normal endometrium. Cell Rep 2018;24:1777-89.
26. Gargett CE, Schwab KE, Brosens JJ, Puttemans P, Benagiano G, Brosens I. Potential role of endometrial stem/progenitor cells in the pathogenesis of early-onset endometriosis. Mol Hum Reprod 2014;20:591-8.
27. Suginami H. A reappraisal of the coelomic metaplasia theory by reviewing endometriosis occurring in unusual sites and instances. Am J Obstet Gynecol 1991; 165:214-8.
28. Jerman LF, Hey-Cunningham AJ. The role of the lymphatic system in endometriosis: a comprehensive review of the literature. Biol Reprod 2015;92:64.
29. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984; 64:151-4.
30. Han SJ, Jung SY, Wu S-P, et al. Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. Cell 2015; 163:960-74.
31. Santamaria X, Mas A, Cervelló I, Taylor H, Simon C. Uterine stem cells: from basic research to advanced cell therapies. Hum Reprod Update 2018;24:673-93.
32. Klemmt PAB, Carver JG, Koninckx P, McVeigh EJ, Mardon HJ. Endometrial cells from women with endometriosis have increased adhesion and proliferative capacity in response to extracellular matrix components: towards a mechanistic model for endometriosis progression. Hum Reprod 2007;22:3139-47.
33. Symons LK, Miller JE, Kay VR, et al. The immunopathophysiology of endometriosis. Trends Mol Med 2018;24:748-62.
34. Bulun SE. Endometriosis. N Engl J Med 2009;360:268-79.
35. Bulun SE, Monsavais D, Pavone ME, et al. Role of estrogen receptor-β in endometriosis. Semin Reprod Med 2012;30: 39-45.
36. Dyson MT, Roqueiro D, Monsivais D, et al. Genome-wide DNA methylation analysis predicts an epigenetic switch for GATA factor expression in endometriosis. PLoS Genet 2014;10(3):e1004158.
37. Burney RO, Talbi S, Hamilton AE, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology 2007;148:3814-26.
38. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 2014;10: 261-75.
39. Mu F, Harris HR, Rich-Edwards JW, et al. A prospective study of inflammatory markers and risk of endometriosis. Am J Epidemiol 2018;187:515-22.
40. Reis FM, Petraglia F, Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. Hum Reprod Update 2013;19: 406-18.
41. Kang Y-J, Jeung IC, Park A, et al. An increased level of IL-6 suppresses NK cell activity in peritoneal fluid of patients with endometriosis via regulation of SHP-2 expression. Hum Reprod 2014;29:2176-89.
42. Beste MT, Pfäffle-Doyle N, Prentice EA, et al. Molecular network analysis of endometriosis reveals a role for c-Jun-regulated macrophage activation. Sci Transl Med 2014;6:222ra16.
43. Laux-Biehlmann A, d'Hooghe T, Zollner TM. Menstruation pulls the trigger for inflammation and pain in endometriosis. Trends Pharmacol Sci 2015;36:270-6.
44. Greaves E, Temp J, Esnal-Zufiurre A, Mechsner S, Horne AW, Saunders PTK. Estradiol is a critical mediator of macrophage-nerve cross talk in peritoneal endometriosis. Am J Pathol 2015;185:2286-97.
45. Forster R, Sarginson A, Velichkova A, et al. Macrophage-derived insulin-like growth factor-1 is a key neurotrophic and nerve-sensitizing factor in pain associated with endometriosis. FASEB J 2019;33: 11210-22.
46. Saha R, Pettersson HJ, Svedberg P, et al. Heritability of endometriosis. Fertil Steril 2015;104:947-52.
47. Treloar SA, Wicks J, Nyholt DR, et al. Genomewide linkage study in 1,176 affected sister pair families identifies a significant susceptibility locus for endometriosis on chromosome 10q26. Am J Hum Genet 2005;77:365-76.
48. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998;62:676-89.
49. Lee SH, Harold D, Nyholt DR, et al. Estimation and partitioning of polygenic variation captured by common SNPs for Alzheimer's disease, multiple sclerosis and endometriosis. Hum Mol Genet 2013; 22:832-41.
50. Visscher PM, Wray NR, Zhang Q, et al. 10 Years of GWAS discovery: biology, function, and translation. Am J Hum Genet 2017;101:5-22.
51. Sapkota Y, Steinthorsdottir V, Morris AP, et al. Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. Nat Commun 2017;8: 15539.
52. Rahmioglu N, Banasik K, Christofidou P, et al. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. bioRxiv. 2018 (https://www.biorxiv.org/content/10.1101/406967v1).
53. Powell JE, Fung JN, Shakhbazov K, et al. Endometriosis risk alleles at 1p36.12 act through inverse regulation of CDC42 and LINC00339. Hum Mol Genet 2016;25: 5046-58.
54. Casper RF. New tools for enhancing collaborative endometriosis research. Fertil Steril 2014;102:1211-2.
55. Wiegand KC, Shah SP, Al-Agha OM, et al. *ARID1A* mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 2010;363:1532-43.
56. Anglesio MS, Papadopoulos N, Ayhan A, et al. Cancer-associated mutations in endometriosis without cancer. N Engl J Med 2017;376:1835-48.
57. Lac V, Nazeran TM, Tessier-Cloutier B, et al. Oncogenic mutations in histologically normal endometrium: the new normal? J Pathol 2019;249:173-81.
58. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet 2018;50:1505-13.
59. Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 2015;47:373-80.
60. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet 2018;50:1219-24.
61. Esserman LJ, WISDOM Study and Athena Investigators. The WISDOM Study: breaking the deadlock in the breast cancer screening debate. NPJ Breast Cancer 2017;3:34.

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62. Nisenblat V, Bossuyt PMM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev 2016;5:CD012179.
63. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400-12.
64. Nisenblat V, Bossuyt PMM, Farquhar C, Johnson N, Hull ML. Imaging modalities for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev 2016;2:CD009591.
65. Ballard K, Lowton K, Wright J. What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. Fertil Steril 2006;86:1296-301.
66. Ballard KD, Seaman HE, de Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study. BJOG 2008;115:1382-91.
67. Nnoaham KE, Hummelshoj L, Kennedy SH, Jenkinson C, Zondervan KT. Developing symptom-based predictive models of endometriosis as a clinical screening tool: results from a multicenter study. Fertil Steril 2012;98(3):692.e5-701.e5.
68. Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril 2017;108:125-36.
69. Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril 2016;106(7):1552.e2-1571.e2.
70. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28-40.
71. Ferrero S, Gillott DJ, Venturini PL, Remorgida V. Use of aromatase inhibitors to treat endometriosis-related pain symptoms: a systematic review. Reprod Biol Endocrinol 2011;9:89.
72. International Association for the Study of Pain. IASP statement on opioids. February 2018 (https://www.iasp-pain.org/Advocacy/Content.aspx?ItemNumber=7194).
73. Horne AW, Daniels J, Hummelshoj L, Cox E, Cooper KG. Surgical removal of superficial peritoneal endometriosis for managing women with chronic pelvic pain: time for a rethink? BJOG 2019;126:1414-6.
74. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000-2004. Am J Obstet Gynecol 2008;198(1):34.e1-34.e7.
75. Brandsborg B, Nikolajsen L. Chronic pain after hysterectomy. Curr Opin Anaesthesiol 2018;31:268-73.
76. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril 2012;98:591-8.
77. Laschke MW, Menger MD. The gut microbiota: a puppet master in the pathogenesis of endometriosis? Am J Obstet Gynecol 2016;215(1):68.e1-68.e4.
78. Hirsch M, Duffy JMN, Barker C, et al. Protocol for developing, disseminating and implementing a core outcome set for endometriosis. BMJ Open 2016;6(12):e013998.

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