

Assessing research gaps and unmet needs in endometriosis



Sawsan As-Sanie, MD, MPH; Rebecca Black, MNM; Linda C. Giudice, MD, PhD; Tanika Gray Valbrun, BS; Jhumka Gupta, ScD; Brittany Jones, MS; Marc R. Laufer, MD; Alexandra T. Milspaw, PhD, MEd; Stacey A. Missmer, ScD; Abby Norman; Robert N. Taylor, MD, PhD; Kedra Wallace, PhD; Zev Williams, MD, PhD; Paul J. Yong, MD, PhD; Rebecca A. Nebel, PhD

Endometriosis, a systemic disease that is often painful and chronic, affects ~10% of reproductive-age women. The disease can have a negative impact on a patient's physical and emotional well-being, quality of life, and productivity. Endometriosis also places significant economic and social burden on patients, their families, and society as a whole. Despite its high prevalence and cost, endometriosis remains underfunded and under-researched, greatly limiting our understanding of the disease and slowing much-needed innovation in diagnostic and treatment options. Due in part to the societal normalization of women's pain and stigma around menstrual issues, there is also a lack of disease awareness among patients, health care providers, and the public. The Society for Women's Health Research convened an interdisciplinary group of expert researchers, clinicians, and patients for a roundtable meeting to review the current state of the science on endometriosis and identify areas of need to improve a woman's diagnosis, treatment, and access to quality care. Comprehensive and interdisciplinary approaches to disease management and increased education and disease awareness for patients, health care providers, and the public are needed to remove stigma, increase timely and accurate diagnosis and treatment, and allow for new advancements.

Key words: chronic pain, endometriosis, infertility, pelvic pain, stigma, women's health

Endometriosis is a painful, chronic, and inflammatory disease that is characterized by the growth of endometrial-like tissue outside of the uterus and affects approximately 10% of reproductive-age women, an estimated 200 million women and teens worldwide.^{1–3} Common symptoms of

this systemic,^{4–6} debilitating disease include variable experience and severity of dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility^{7–9} as well as back pain and bladder or bowel problems (eg, painful urination or bowel movements).^{7,8,10–12} Other individuals are asymptomatic.^{7,11,13}

Prevalence of endometriosis is highest in women with infertility or chronic pelvic pain, reaching 25–50% and 71–87%, respectively.^{2,3,9} Although data are limited, there is some evidence that approximately 40% of adult cases show spontaneous regression of disease in follow-up studies a few months after initial examination.¹⁴ However, longer-term follow-up studies in baboons, which have spontaneous endometriosis similar to humans, suggest that endometriosis is a progressive disease, with periods of regression.¹⁵

Although the cardinal symptoms of endometriosis are pelvic symptoms, comorbidities are very common in

From the Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI (Dr As-Sanie); patient advocates (Ms Black, Fairfax, VA and Ms Norman, Camden, ME); the Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco, CA (Dr Giudice); the White Dress Project, Atlanta, GA (Ms Gray Valbrun); the Department of Global and Community Health, George Mason University, Fairfax, VA (Dr Gupta); the Society for Women's Health Research, Washington, DC (Dr Nebel and Ms Jones); the Division of Gynecology, Boston Children's Hospital (Dr Laufer), the Division of Pediatric and Adolescent Gynecology, Brigham and Women's Hospital (Dr Laufer), and the Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston, MA (Dr Laufer); 4Directions Counseling LLC, Bethlehem, PA (Dr Milspaw); the Department of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, East Lansing, MI (Dr Missmer) and the Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA (Dr Missmer); the Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT (Dr Taylor); the Department of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS (Dr Wallace); the Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY (Dr Williams); and the Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada (Dr Yong).

Received Oct. 22, 2018; revised Feb. 11, 2019; accepted Feb. 14, 2019.

This work was supported by a programmatic grant from AbbVie Inc.

Dr As-Sanie is a consultant to AbbVie Inc and Myovant Sciences and is an author for UpToDate, Inc. Dr Giudice is a consultant to AbbVie Inc, Myovant Sciences, ForEndo, and NextGen Jane. Dr Laufer receives research funding from the Marriott Foundations, is an author for UpToDate, Inc, serves on the International Advisory Board of AbbVie Inc, and is an advisor to NextGen Jane. Dr Missmer serves on advisory boards for AbbVie Inc and Celmatix, is an unfunded collaborator to Oratel Diagnostics, and receives research funding from Marriott Foundations and AbbVie Inc. Dr Norman is author of *Ask Me About My Uterus: A Quest to Make Doctors Believe in Women's Pain*. Dr Taylor is a consultant to AbbVie Inc and ObsEva. Dr Williams serves as a consultant and is on the speaker's bureau for AbbVie Inc. The other authors report no conflict of interest.

Corresponding author: Rebecca A. Nebel, PhD. science@swhr.org

0002-9378/\$36.00 • © 2019 Elsevier Inc. All rights reserved. • <https://doi.org/10.1016/j.ajog.2019.02.033>

women with endometriosis. Nearly 95% of women with endometriosis reported at least 1 or more comorbid disorders, such as migraine, depression, anxiety, irritable bowel syndrome (IBS), interstitial cystitis/painful bladder syndrome, chronic fatigue syndrome, fibromyalgia, uterine fibroids, and ovarian cysts.^{16–20}

Endometriosis is also associated with increased risk for several types of cancer (ovarian, breast, cutaneous melanoma), systemic lupus erythematosus, rheumatoid arthritis, and cardiovascular disease.^{21–24}

Endometriosis can negatively affect all aspects of a patient's daily life, including sexual relations, appetite, exercise, sleep, emotional well-being, social activities, child care, and work and household productivity.^{25–28} Total workplace productivity loss averages 6.3 hours per week, with the majority of that loss caused by presenteeism, while total household productivity loss averages 4.9 hours per week.²⁹

Endometriosis is also costly, at an estimated \$69.4 billion per year in excess health expenditures in the United States.^{2,30} Estimated direct costs in the United States are \$12,118 per patient per year.³¹ Claims data show that average annual health care costs (medical and prescription) are more than 3 times higher for women with endometriosis compared with patients without endometriosis, even 5 years before and 5 years after diagnosis.^{2,18,30}

Annual health care costs for women with endometriosis treated in referral centers are similar to costs for other chronic diseases that receive more resources such as diabetes, Crohn's disease, and rheumatoid arthritis.³⁰ Endometriosis-associated costs can be greater, depending on the severity of disease, presence of pelvic pain, and presence of infertility.³⁰

Despite the prevalence of endometriosis and its significant burden on women, their families, society, and the health care system, the disease is underfunded and underresearched.³² As such, scientific progress has been slow, and diagnostic and treatment options remain limited. Societal factors such as clinical gender bias and inequities in the treatment of

pain based on gender have been well documented^{33–36} and may contribute to the underprioritization of endometriosis research funding. Furthermore, endometriosis symptoms that are associated with menstruation, infertility, and/or bowel issues are often met with societal stigma^{37–40} and thus may further complicate addressing this disease.

To this end, the Society for Women's Health Research (SWHR), a nearly 30-year-old nonprofit organization, convened an interdisciplinary expert group of researchers, clinicians, and patients for a roundtable meeting to evaluate both diagnostics and treatment in endometriosis. The goals of the meeting were as follows: (1) review current practice, (2) reflect on the barriers affecting diagnosis and treatment, and (3) highlight research priorities for the future of endometriosis care. In the following text, we summarize discussions from the roundtable.

Materials and Methods

SWHR designed the roundtable to create an interactive dialogue between thought leaders in the field, including researchers, clinicians, patients, industry, and government officials. SWHR selected participants with diverse perspectives with regard to expertise, training, background, gender, and geographic location. Discussions with meeting attendees prior to the roundtable identified topics that experts considered top priorities to address in an interdisciplinary setting.

An SWHR facilitator moderated the roundtable, and patients gave personal testimonies, which organically led to discussion among the group. A transcriptionist captured minutes from the meeting, and these minutes were used to identify themes, including barriers to diagnosis and treatment and priorities for the future, that informed the structure of this paper.

Diagnostics

Laparoscopic visualization with or without histologic confirmation is currently the only way to definitively diagnose endometriosis and remains the gold standard for diagnosis in

clinical guidelines from many national and international professional societies, including the American College of Obstetricians and Gynecologists, the European Society of Human Reproduction and Embryology, the World Endometriosis Society, the National Institute for Health and Care Excellence, the Society of Obstetricians and Gynaecologists of Canada, and the American Society for Reproductive Medicine.^{9,41–45}

Most of these guidelines have not been updated within the past 5–10 years, although guidelines from the aforementioned groups and many experts in the field state that definitive diagnosis is not always required before initiating medical therapy.^{46,47} Like with most surgeries, laparoscopy is invasive and comes with its own risks, plus economic and geographic barriers may limit patients' access.^{2,47}

Barriers to diagnosis

Diagnostic delays remain a significant barrier to receiving timely and appropriate care for endometriosis. On average, women experience a delay of 7–12 years from the onset of pain symptoms to a surgical diagnosis.^{28,48} The delay for patients seeking help caused by pelvic pain is longer than the delay for those seeking help caused by infertility.^{49,50} Delays in diagnosis can degrade the patient-provider relationship, cause physical and emotional damage, impair quality of life, and add to the significant personal and societal costs associated with the disease.^{28,51,52}

Societal barriers and the role of stigma

Stigma around menstrual issues and societal normalization of women's pain play a pivotal role in diagnostic delay. One study found women wait on average 2.3 years from the onset of symptoms before seeking help.⁴⁸ Women may not recognize their pain as a treatable condition, especially if this pain began at menarche.⁵³ Societal normalization of women's pain and the taboo around topics like menstruation or painful sex can prevent women from seeking care or discussing symptoms with and receiving

support from friends, family, and health care providers (HCPs).³⁸

Barriers related to understanding of the disease

The etiology of endometriosis is not fully understood. Retrograde menstruation, coelomic metaplasia, genetics, immune dysfunction, oxidative stress and inflammation, and stem cells are all thought to play a role in the pathogenesis of the disease.^{6,54,55} Some experts argue endometriosis should be considered an amalgamation of disorders because of the diversity of symptoms and symptom severity as well as differences in lesion types (eg, superficial peritoneal endometriosis, deep infiltrating endometriosis, ovarian endometriomas, extrapelvic endometriosis).^{42,56}

This lack of clear understanding about the disease's etiology and the spectrum of symptoms, including gynecologic and nongynecologic issues, can also contribute to diagnostic delay.

For example, chronic pelvic pain, the most commonly reported symptom of endometriosis, is not specific to endometriosis. Other gynecologic diseases such as pelvic inflammatory disease, uterine fibroids, and adenomyosis, as well as nongynecologic diseases including IBS, interstitial cystitis/painful bladder syndrome, and fibromyalgia, can have symptoms that overlap with those common in endometriosis.⁴⁴ The process of ruling out these other diseases can contribute to delays in diagnosis and treatment of endometriosis. Furthermore, these conditions are highly comorbid with endometriosis, so delays can occur if HCPs do not recognize that endometriosis can coexist with other pain conditions, particularly if symptoms persist.

Provider-related barriers

On average, women with endometriosis make 7 visits to their primary HCP before being referred to specialists,²⁸ and nearly three-quarters of women experience a misdiagnosis.⁴⁸ In addition, the short time allotted for HCP visits may not allow for adequate evaluation.⁵⁷

One survey of general HCPs found that half could not name 3 of the main

symptoms of endometriosis. Additionally, nearly two-thirds did not feel comfortable in the diagnosis and follow-up of women presenting with endometriosis.⁵⁸ This can have serious implications because only 24% of surveyed practitioners made referrals without delay of additional examinations when endometriosis was suspected.⁵⁸

Another survey of gynecologists found nearly 50% believed that earlier diagnosis of endometriosis cannot prevent the course of the disease because there is no effective treatment.⁵¹ This survey demonstrates that HCPs may not make a referral to a specialist, even if endometriosis is suspected, despite the fact that evidence suggests diagnostic delays cause physical, emotional, and social harm for patients.⁵³

Stigma also plays a role in provider-related delayed diagnosis. HCPs may trivialize symptoms, be quick to dismiss symptoms as normal, or feel uncomfortable discussing symptoms with their patients, particularly younger women, who on average have a longer delay in diagnosis.⁴⁹

There is currently no validated set of screening questions routinely used for HCPs to ask women about their menstrual pain, even though implementing this practice could facilitate earlier diagnosis of endometriosis and other causes of pelvic pain.^{59,60} Standardized screenings, such as those used to identify violence against women during a well-woman visit, could be used as a model in screening for endometriosis. Taken together, inadequate HCP training and societal normalization of menstrual pain create significant barriers for patients in need of referrals to specialists when endometriosis is suspected.

Barriers with current diagnostic tools

In addition to the lack of disease awareness and education, the absence of noninvasive or less invasive diagnostic tools (eg, biomarkers, radiologic imaging) may contribute to diagnostic delay. One survey found that nearly two-thirds of gynecologists agreed there was a significant delay in diagnosing endometriosis, which they partly attributed to the absence of a valid noninvasive diagnostic

test.⁵¹ This suggests that the invasiveness of laparoscopic surgery itself may be one reason HCPs delay diagnosis. Lack of access to a specialist with expertise in laparoscopic surgery for endometriosis and/or insurance coverage also remain critical barriers.⁵⁷

Young women in particular face extended delays from the time they first speak to their HCP about symptoms to receiving a diagnosis of endometriosis. One study found that women under the age of 19 years waited on average 12 years.⁴⁹ One possible explanation is that teens, parents, and primary care providers may be hesitant to see/refer to a gynecologist because of feeling uneasy about gynecologic pelvic examinations in a non-sexually active young woman. Furthermore, some HCPs are reluctant to recommend or perform an invasive diagnostic procedure, like a laparoscopy, in young girls.^{61,62}

The current gold standard guidelines for diagnosing endometriosis examine only whether endometrial lesions are present. The most commonly used disease staging system is also based on the location and amount of lesions within the pelvic cavity.⁶³ However, most evidence has demonstrated there is only a marginal relationship among the number of lesions, the severity of disease, its symptoms, and overall impact on quality of life (except for a correlation between deep infiltrating endometriosis sites and some types of pelvic pain).⁶⁴

For example, a woman with revised American Society for Reproductive Medicine stage 4 endometriosis, which is considered severe, may experience fewer life-disrupting symptoms than a woman with stage 1 endometriosis, which is classified as minimal, suggesting that these adjectives should not be used interchangeably with the numeric stages of disease. Furthermore, current diagnostic and disease-staging guidelines provide little predictive value regarding outcomes (eg, pain relief or fertility) or recurrence risk.^{65–67} This may be in part because the current approach does not take into account the inflammatory and systemic nature of the disease or the rare but

burdensome presence of extrapelvic endometriosis.

Requiring a laparoscopy to receive a definitive diagnosis can also greatly impede research if women's participation in research requires a history of disease documented by surgery. This can create a selection bias in clinical research studies, particularly if comparisons are to women who underwent laparoscopies for other indications, for which there may be overlapping etiology. It also greatly precludes population-based studies, which in turn has limited our understanding of the disease and the patient populations it affects.

Future of endometriosis diagnostics

Because of the invasiveness and costliness of laparoscopy, noninvasive diagnostics for endometriosis in both clinical practice and research are greatly needed. Presently there are some noninvasive and less invasive tools that may help identify certain types of endometrial lesions. For example, transvaginal ultrasounds or magnetic resonance imaging can be used to diagnose ovarian endometriomas and deeply infiltrative endometriosis, such as lesions involving the bladder, rectovaginal septum, and sigmoid colon.⁶⁸ Sensitivity and specificity rates for non-ovarian endometriosis using transvaginal ultrasound are 78–98% and 90–100%, respectively.⁵¹

Transvaginal ultrasounds are not reliable diagnostic aids for superficial peritoneal disease, which is the most common type of endometriosis. Importantly, diagnostic accuracy is lower if imaging is not performed by individuals with appropriate training, which can limit its usefulness because many sonographers do not receive endometriosis-specific training.^{69,70} However, many studies have shown that competency greatly improves after brief training programs,^{70–73} suggesting a new avenue for increasing the number of experts available and thereby increasing women's access to state-of-the-art imaging for endometriosis.

In addition, researchers are exploring the use of biomarkers for early diagnosis

as a noninvasive approach, but more investment in this area is needed for it to be fruitful. Current blood-based biomarkers under investigation include regulators of gene expression (micro-RNAs), inflammatory markers, tumor markers, growth factors, and hormonal markers as well as endometrial and menstrual effluent biomarkers.^{74,75} However, none of these tests have been validated in large heterogeneous samples nor have they been proved to have adequate sensitivity and specificity to be used clinically outside a research setting. Testing of biomarkers on populations that reflect the diversity of those with the disease is needed.

Given the heterogeneity of endometriosis and multiple pathways that are involved in the etiology of the disease, there may not be 1 universal biomarker that can accurately diagnose all forms of the disease. A combination of multiple biomarkers may be necessary to diagnose the disease or define different subtypes of endometriosis, which would open up avenues for more personalized treatments. However, discerning this information will require large, diverse, and highly phenotyped patient populations, with detailed prospective data collection on severity and characteristics of pelvic symptoms (eg, dysmenorrhea, nonmenstrual pain, dyspareunia, infertility), associated comorbidities (eg, other pain conditions, autoimmune disease), and location, appearance, and extent of lesions.

Organizations such as the World Endometriosis Research Foundation (WERF) have already begun taking steps to achieve this. The foundation's Endometriosis Phenome and Biobanking Harmonisation Project was established to standardize the reporting and pathological processing for endometriosis research and facilitate large-scale international collaborations to advance understanding of the disease.^{76–78}

Treatment

There is currently no cure for endometriosis. Because symptoms can appear as early as menarche, management of the disease may span decades, including the optimal years for trying to conceive.

Current strategies to manage endometriosis include medical and surgical treatments as well as complementary approaches designed with the primary goal of managing pain and associated symptoms and possibly restoring fertility.^{8,42}

Pain and infertility are 2 of the most common reasons women seek treatment for endometriosis, and the treatment approaches differ for each. Considerations for different treatment types with respect to age, disease severity, and desire to preserve fertility are reviewed elsewhere.^{8,9}

First-line medical therapies for endometriosis include nonsteroidal antiinflammatory drugs, combined estrogen-progestin hormonal contraceptives (cyclic or preferably continuous), and progestins (oral, injectable, implants, intrauterine device). Most clinicians consider first-line medical therapies as those that are low cost, well tolerated, efficacious, and easily accessible.⁴² Second-line medical treatments have equal efficacy but are more costly and/or have side effects. These include gonadotrophin-releasing hormone agonists and antagonists (with or without add-back hormone replacement therapy) or danazol, an androgenic steroid.

Laparoscopy with excision or destruction of superficial lesions and excision of deep lesions can be a first-line or second-line surgical approach for treating pain.⁸ Guidelines recommend excision surgeries be performed by surgeons who specialize in this type of surgery.⁴² Surgeries that interrupt nerve pathways (eg, presacral neurectomy) or hysterectomy (with or without oophorectomy) are third- or fourth-line approaches that are used after other treatment options have failed.⁸ However, even these procedures are not curative and pain can recur, often without evidence of recurrent endometriosis lesions.⁶

Comorbidities are highly prevalent in women with endometriosis.⁷⁹ Thus, multimodal approaches to the evaluation and treatment of chronic pain and associated symptoms, including non-pharmacologic therapies, are an important part of a comprehensive strategy for

managing endometriosis. For example, physical therapists with specialty in treating pelvic floor dysfunction may be beneficial for women with associated myofascial pain.^{80,81} Furthermore, two randomized controlled trials found acupuncture to provide some patients with relief from endometriosis-related pain.^{82,83} A randomized control trial examining the use of yoga found similar effects.⁸⁴

Additionally, mental health professionals can play an important role in addressing issues such as depression and grieving that are associated with the disease as well as provide cognitive behavioral therapy techniques such as coping and relaxation strategies.^{44,80,81,85}

Barriers to treatment

Limitations of current therapies

Available medical therapies provide relief from endometriosis-related pain for many women, but not all.⁸⁶ On average, 11–19% of women report no improvement in pain with medical therapy, and 5–59% report some degree of persistent pain at the end of a treatment period.⁸⁶ Discontinuation rates for medical treatments range from 5–16% because of significant side effects, such as bone loss, hot flashes, and weight gain, or limited efficacy, restricting their usefulness or longevity.^{8,41,86} Recurrent pain is common after treatment cessation, with 17–34% of women reporting recurrence of pain after stopping treatment.⁸⁶

Many medical therapies (eg, combined hormonal contraceptives, progestins, and gonadotropin-releasing hormone agonists and antagonists) cannot be used when women are trying to get pregnant.^{7,42} This forces many women with endometriosis who want to become pregnant to choose between minimizing debilitating pain with medication and timing their attempts to conceive while off of their medication.

After laparoscopy, disease recurrence rates range from 30–50%,⁸ with up to 55% of women undergoing an additional surgery within 7 years.⁸⁷ Approximately 20% of women may not show improvement after initial surgery.⁸⁸

Even hysterectomy is not a cure for all women with endometriosis. In women

with endometriosis who underwent a hysterectomy during which both ovaries were preserved, 7.3% underwent reoperation within 2 years because of recurrence of pelvic pain, and 21.6% underwent reoperation within 7 years.⁸⁷ Reoperation rates for women who underwent hysterectomy and bilateral oophorectomy were 4% by year 2 and 8.3% by year 7 after the hysterectomy. Furthermore, reoperation rates can vary by age at hysterectomy. While bilateral oophorectomy was associated with a lower reoperation rate in women older than 40 years old, the incidence of reoperation with bilateral oophorectomy (compared with ovarian preservation) was not lower in women aged 30–39 years. This suggests that many, but not all, women experience symptom relief following hysterectomy.

Furthermore, these reoperation rates only capture pain remediation failure among women who return to the same surgeon and undergo reoperation; data are lacking on those who have pain return but discontinue engagement with that HCP and for those who do return to that HCP but are treated without reoperation. Therefore, these pain recurrence rates are likely an underestimate.

Incomplete excision of lesions, central sensitization, and underrecognized or undertreated comorbid conditions (eg, pelvic floor myofascial pain, interstitial cystitis, or IBS) are likely some of the reasons that symptoms can reoccur following a hysterectomy, necessitating the need for additional surgery.^{89,90} In addition, undergoing a hysterectomy has its own health risks that extend beyond those related to reproductive health.^{24,91–93}

Current medical and surgical options for endometriosis aim at suppressing or eliminating lesions in the pelvic cavity.⁶ However, the relationship between lesions and symptoms (eg, pain and infertility) is not well established or understood.⁶⁷ Pain can persist or recur after surgery and recurrent symptoms do not necessarily correlate with recurrent lesions. Furthermore, while medical and surgical therapies can be effective in alleviating endometriosis-related pain and fertility issues, they are not always

effective and also do not address all the symptoms associated with endometriosis, such as the fatigue, mood disorders, or pain outside the pelvis.

Barriers in accessing care

In addition to the lengthy diagnostic delay discussed above, high costs, insurance issues, stigma, lack of HCP education, and access to specialists can all create barriers to receiving care.

In one survey of young women with chronic pelvic pain, they cited difficulty with insurance coverage, lack of HCP knowledge or training, and difficulty getting appointments with specialists as the main factors impeding their attempts to receive optimal care.⁹⁴

Additionally, some employers may not be knowledgeable about endometriosis and therefore may be quick to trivialize or assume women are making up or exaggerating the severity of their symptoms.^{95,96} Unsupportive work environments can make it difficult for women to use sick leave, receive an appropriate amount of sick leave, or take time off for HCP appointments.^{27,95,97} This can greatly affect productivity and overall quality of life at work.

Provider-related barriers

As of 2017, there were 35,586 general obstetrician-gynecologists in the United States.⁵⁷ However, obstetrician-gynecologists are not evenly distributed geographically. Nearly 50% of counties in the United States, in predominantly rural areas, lack a single obstetrician-gynecologist.⁵⁷ This leaves the approximately 10 million women who reside in these counties without ready access to an obstetrician-gynecologist. Of the general obstetrician-gynecologists, an even smaller percentage specialize in the treatment and management endometriosis, which is imperative for proper care.

Furthermore, the lack of education about endometriosis and chronic pelvic pain for HCPs may result in unnecessary and invasive procedures. A common misbelief is that a hysterectomy can cure endometriosis, which (as discussed in detail in the previous text) is not necessarily true. This can cause HCPs to suggest hysterectomy as

a first- or second-line treatment option, even though guidelines recommend hysterectomies be considered a last-line approach for only severe and refractory cases.

Endometriosis is the second leading indication for hysterectomy in the United States (the first is uterine fibroids and/or abnormal bleeding). Endometriosis accounts for 17.7% of all hysterectomies and is the leading cause of hysterectomy among women 30–34 years old.⁹⁸ Black women are disproportionately more likely than white women to undergo hysterectomy for benign gynecological conditions and are more likely to have complications from surgery.⁹⁹

Future of endometriosis treatments

Current medical and surgical treatment options focus on suppressing lesion proliferation in hopes of eliminating pain and/or infertility, even though the relationship between lesions and these symptoms is not well understood. Future treatments and care should shift toward a patient-centric, multidisciplinary approach that focuses on the patient as a whole, rather than 1 symptom at a time.

Centers of excellence, specialized programs that provide capability and resources related to a particular medical area, offer 1 type of patient-centric model for treating and managing endometriosis. Centers of excellence in endometriosis take an interdisciplinary approach to patient care with a team that includes experts in laparoscopy, medical management, pain education, physical therapy, and psychology.¹⁰⁰

A recent prospective study from a center of excellence for chronic pelvic pain in Canada found that its interdisciplinary approaches were successful in lessening pain, reducing emergency room and physician visits, decreasing the prevalence of comorbid conditions, and improving functional quality of life.¹⁰⁰ The implementation of comprehensive treatment strategies, like those in centers of excellence, that address all the needs of the patient, including quality-of-life issues, is imperative.

In addition, current care for women with endometriosis is sometimes

based on low-value care tests and procedures, meaning they have defined harm, uncertain benefits, or effectiveness that is no better than less expensive alternatives.¹⁰¹ Given the economic burden of endometriosis, moving toward care that is based on the best available data and funding studies that increase this knowledge base remains a priority.

More research is also needed to better understand the underlying biology of endometriosis and possible endometriosis subtypes, which could lead to new therapeutic avenues and more individualized treatment plans. Of particular interest are alternatives to hormonal therapy for those patients who are intolerant to current hormonal regimens because of side effects as well as patients who are trying to conceive.

Nonhormonal options, such as those modulating angiogenesis or neuroinflammation, are urgently needed.¹⁰² Moreover, future treatments should aim to address the issues most important to patients, and future clinical trials should utilize patient-reported outcomes and include current first-line medications as a comparator when possible.¹⁰¹

Increased funding is necessary to accomplish these goals. Despite the high prevalence and impact of endometriosis, the National Institutes of Health funding for the disease in 2018 was \$7 million, near the bottom of the agency's 285 funded disease/research areas.⁵² Insufficient funding means fewer researchers have the opportunity to study endometriosis, further impeding the advancements that are needed in the field.

Conclusion

Endometriosis places a significant burden on teens and adult women, their families, and society as a whole, yet the stigma surrounding the disease and societal normalization of women's pain continue to preclude fast and accurate diagnosis, effective treatment, and innovation in the field.

The gold standard diagnostic is invasive and costly, although research into noninvasive diagnostics is underway.⁴⁷

Currently, medical and surgical therapies focus on treating lesions, but often do not address the negative impact endometriosis has on a woman's quality of life. Comprehensive and interdisciplinary approaches that take patients' holistic needs into account are needed, along with more research that can give insight into the underlying biology of the disease, enable new therapies, and create high-quality evidence to help improve care.

Evidence-based public health campaigns could also improve disease knowledge among patients, HCPs, and the public. Such campaigns, as well as more training for providers, could also address the stigma associated with endometriosis and improve social support for those experiencing the disease.³⁸ The Society for Women's Health Research is committed to improving education and awareness around endometriosis and other conditions that disproportionately, differently, or exclusively affect women to improve diagnosis, treatment, and access to quality care. ■

ACKNOWLEDGMENT

We sincerely thank Emily Ortman from the Society for Women's Health Research for helping review and edit the manuscript.

REFERENCES

1. Adamson GD, Kennedy S, Hummelshoj L. Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. *J Endometriosis* 2010;2:3–6.
2. Soliman AM, Surrey E, Bonafede M, Nelson JK, Castelli-Haley J. Real-world evaluation of direct and indirect economic burden among endometriosis patients in the United States. *Adv Ther* 2018;35:408–23.
3. Shafrir A, Farland L, Shah D, et al. Risk for and consequences of endometriosis: a critical epidemiologic review. *Best Pract Res Clin Obstet Gynaecol* 2018;51:1–15.
4. Alderman MH III, Yoder N, Taylor HS. The systemic effects of endometriosis. *Sem Reprod Med* 2017;35:263–70.
5. Naqvi H, Mamillapalli R, Krikun G, Taylor HS. Endometriosis located proximal to or remote from the uterus differentially affects uterine gene expression. *Reprod Sci* 2016;23:186–91.
6. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Vignano P. Endometriosis. *Nat Rev Dis Primers* 2018;4:9.

7. Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. *J Assist Reprod Genet* 2010;27:441–7.
8. Giudice LC. Clinical practice. Endometriosis. *N Engl J Med* 2010;362:2389–98.
9. American College of Obstetricians and Gynecology. Management of endometriosis. ACOG Practice bulletin no. 114. *Obstet Gynecol* 2010;116:225–36.
10. Fourquet J, Sinaii N, Stratton P, et al. Characteristics of women with endometriosis from the USA and Puerto Rico. *J Endometr Pelvic Pain Disord* 2015;7:129–35.
11. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am* 2012;39:535–49.
12. DiVasta AD, Vitonis AF, Laufer MR, Missmer SA. Spectrum of symptoms in women diagnosed with endometriosis during adolescence vs adulthood. *Am J Obstet Gynecol* 2018;218:324.e1–11.
13. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997;24:235–58.
14. Evers JH. Is adolescent endometriosis a progressive disease that needs to be diagnosed and treated? *Hum Reprod* 2013;28:2023.
15. D'Hooghe TM, Bambra CS, Raeymaekers BM, Koninckx PR. Serial laparoscopies over 30 months show that endometriosis in captive baboons (*Papio anubis*, *Papio cynocephalus*) is a progressive disease. *Fertil Steril* 1996;65:645–9.
16. Cavaggioni G, Lia C, Resta S, et al. Are mood and anxiety disorders and alexithymia associated with endometriosis? A preliminary study. *Biomed Res Int* 2014;2014:786830.
17. Jess T, Frisch M, Jorgensen KT, Pedersen BV, Nielsen NM. Increased risk of inflammatory bowel disease in women with endometriosis: a nationwide Danish cohort study. *Gut* 2012;61:1279–83.
18. Fuldeore M, Yang H, Du EX, Soliman AM, Wu EQ, Winkel C. Healthcare utilization and costs in women diagnosed with endometriosis before and after diagnosis: a longitudinal analysis of claims databases. *Fertil Steril* 2015;103:163–71.
19. Klein S, D'Hooghe T, Meuleman C, Dirksen C, Dunselman G, Simoons S. What is the societal burden of endometriosis-associated symptoms? a prospective Belgian study. *Reprod Biomed Online* 2014;28:116–24.
20. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod* 2002;17:2715–24.
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. Harris HR, Costenbader KH, Mu F, et al. Endometriosis and the risks of systemic lupus erythematosus and rheumatoid arthritis in the Nurses' Health Study II. *Ann Rheum Dis* 2016;75:1279–84.
23. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Forman JP, Missmer SA. Association between endometriosis and hypercholesterolemia or hypertension. *Hypertension* 2017;70:59–65.
24. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and risk of coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2016;9:257–64.
25. Fourquet J, Gao X, Zavala D, et al. Patients' report on how endometriosis affects health, work, and daily life. *Fertil Steril* 2010;93:2424–8.
26. Jones G, Jenkinson C, Kennedy S. The impact of endometriosis upon quality of life: a qualitative analysis. *J Psychosom Obstet Gynaecol* 2004;25:123–33.
27. Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on women's lives: a qualitative study. *BMC Womens Health* 2014;14:123.
28. 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;96:366–73.e8.
29. Soliman AM, Coyne KS, Gries KS, Castelli-Haley J, Snabes MC, Surrey ES. The Effect of endometriosis symptoms on absenteeism and presenteeism in the workplace and at home. *J Manag Care Spec Pharm* 2017;23:745–54.
30. Simoons 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.
31. Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. *Hum Reprod* 2016;31:712–22.
32. National Institutes of Health. Estimates of funding for various research, condition, and disease categories (RCDC) 2018. Available at: https://report.nih.gov/categorical_spending.aspx. Accessed July 5, 2018.
33. Chen EH, Shofer FS, Dean AJ, et al. Gender disparity in analgesic treatment of emergency department patients with acute abdominal pain. *Acad Emerg Med* 2008;15:414–8.
34. Clerc Liaudat C, Vaucher P, De Francesco T, et al. Sex/gender bias in the management of chest pain in ambulatory care. *Womens Health* 2018;14:1745506518805641.
35. Earp BD, Monrad JT, LaFrance M, Bargh JA, Cohen LL, Richeson JA. Gender bias in pediatric pain assessment. *J Pediatr Psychol* 2019;44:403–14.
36. Samulowitz A, Gremyr I, Eriksson E, Hensing G. "Brave men" and "emotional women": a theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain. *Pain Res Manag* 2018;2018:6358624.
37. Earnshaw VA, Quinn DM, Park CL. Anticipated stigma and quality of life among people living with chronic illnesses. *Chronic Illn* 2012;8:79–88.
38. Gupta J, Cardoso LF, Harris CS, et al. How do adolescent girls and boys perceive symptoms suggestive of endometriosis among their peers? Findings from focus group discussions in New York City. *BMJ Open* 2018;8:e020657.
39. Jansen NA, Saint Onge JM. An internet forum analysis of stigma power perceptions among women seeking fertility treatment in the United States. *Soc Sci Med* 2015;147:184–9.
40. Taft TH, Bedell A, Naftaly J, Keefer L. Stigmatization toward irritable bowel syndrome and inflammatory bowel disease in an online cohort. *Neurogastroenterol Motil* 2017;29.
41. Dunselman G, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014;29:400–12.
42. Johnson NP, Hummelshoj L. Consensus on current management of endometriosis. *Hum Reprod* 2013;28:1552–68.
43. Leyland N, Casper R, Laberge P, Singh SS. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can* 2010;32(7 Suppl 2):S1–32.
44. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertil Steril* 2014;101:927–35.
45. Kuznetsov L, Dworzynski K, Davies M, Overton C. Diagnosis and management of endometriosis: summary of NICE guidance. *BMJ* 2017;358:j3935.
46. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol* 2019;220:354.e1–12.
47. Taylor HS, Adamson GD, Diamond MP, et al. An evidence-based approach to assessing surgical versus clinical diagnosis of symptomatic endometriosis. *Int J Gynaecol Obstet* 2018;142:131–42.
48. Hudelist G, Fritzer N, Thomas A, et al. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Hum Reprod* 2012;27:3412–6.
49. Arruda M, Petta C, Abrao M, Benetti-Pinto C. Time elapsed from onset of symptoms to diagnosis of endometriosis in a cohort study of Brazilian women. *Hum Reprod* 2003;18:756–9.
50. Dmowski WP, Lesniewicz R, Rana N, Pepping P, Noursalehi M. Changing trends in the diagnosis of endometriosis: a comparative study of women with pelvic endometriosis presenting with chronic pelvic pain or infertility. *Fertil Steril* 1997;67:238–43.
51. Weintraub A, Soriano D, Seidman D, Goldenberg M, Eisenberg V. Think endometriosis: delay in diagnosis or delay in referral to adequate treatment. *J Fertil In Vitro IVF Worldw Reprod Med Genet Stem Cell Biol* 2014;2:127.
52. Youngster M, Laufer MR, Divasta AD. Endometriosis for the primary care physician. *Curr Opin Pediatr* 2013;25:454–62.
53. 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.

54. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril* 2012;98:511–9.
55. Sourial S, Tempest N, Hapangama DK. Theories on the pathogenesis of endometriosis. *Int J Reprod Med* 2014;2014:179515.
56. Acien P, Velasco I. Endometriosis: a disease that remains enigmatic. *ISRN Obstet Gynecol* 2013;2013:242149.
57. American College of Obstetricians and Gynecologists. The Obstetrician-Gynecologist Workforce in the United States: facts, figures, and implications, 2017. 2017. <https://www.acog.org/~/media/BB3A7629943642ADA47058D0BDCD1521.pdf>.
58. Quibel A, Puscasiu L, Marpeau L, Roman H. General practitioners and the challenge of endometriosis screening and care: results of a survey. *Gynecol Obstet Fertil* 2013;41:372–80.
59. DiBenedetti DB, Soliman AM, Ervin C, et al. Development of the painful periods screening tool for endometriosis. *Postgrad Med* 2018;130:694–702.
60. Surrey E, Carter CM, Soliman AM, Khan S, DiBenedetti DB, Snabes MC. Patient-completed or symptom-based screening tools for endometriosis: a scoping review. *Arch Gynecol Obstet* 2017;296:153–65.
61. Benagiano G, Guo SW, Puttemans P, Gordts S, Brosens I. Progress in the diagnosis and management of adolescent endometriosis: an opinion. *Reprod Biomed Online* 2018;36:102–14.
62. Yeung P Jr, Gupta S, Gieg S. Endometriosis in adolescents: a systematic review. *J Endometr Pelvic Pain Disord* 2017;9:17–29.
63. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817–21.
64. Fauconnier A, Chapron C, Dubuisson JB, Vieira M, Dousset B, Breart G. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. *Fertil Steril* 2002;78:719–26.
65. Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. *Hum Reprod Update* 2011;17:327–46.
66. Vercellini P, Fedele L, Aimi G, De Giorgi O, Consonni D, Crosignani PG. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. *Hum Reprod* 2006;21:2679–85.
67. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: a multivariate analysis of over 1000 patients. *Hum Reprod* 2007;22:266–71.
68. Kinkel K, Frei KA, Balleyguier C, Chapron C. Diagnosis of endometriosis with imaging: a review. *Eur Radiol* 2006;16:285–98.
69. Fraser MA, Agarwal S, Chen I, Singh SS. Routine vs. expert-guided transvaginal ultrasound in the diagnosis of endometriosis: a retrospective review. *Abdom Imaging* 2015;40:587–94.
70. Menakaya UA. Capacity building in endometriosis ultrasound: are we there yet? *Australas J Ultrasound Med* 2015;18:129–31.
71. Guerriero S, Pascual MA, Ajossa S, et al. Learning curve for the ultrasonographic diagnosis of deep endometriosis using a structured off-line training program. *Ultrasound Obstet Gynecol* 2018 Nov 13. <https://doi.org/10.1002/uog.20176>. [Epub ahead of print].
72. Piessens S, Healey M, Maher P, Tsaltas J, Rombauts L. Can anyone screen for deep infiltrating endometriosis with transvaginal ultrasound? *Aust N Z J Obstet Gynaecol* 2014;54:462–8.
73. Tammaa A, Fritzer N, Strunk G, Krell A, Salzer H, Hudelist G. Learning curve for the detection of pouch of Douglas obliteration and deep infiltrating endometriosis of the rectum. *Hum Reprod* 2014;29:1199–204.
74. Agrawal S, Tapmeier T, Rahmioglu N, Kirtley S, Zondervan K, Becker C. The miRNA mirage: how close are we to finding a non-invasive diagnostic biomarker in endometriosis? A systematic review. *Int J Mol Sci* 2018;19:599.
75. Nisenblat V, Bossuyt PM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. *Cochrane Database Syst Rev* 2016:CD012179.
76. Becker CM, Laufer MR, Stratton P, et al. World endometriosis research foundation endometriosis phenome and biobanking harmonisation project: I. Surgical phenotype data collection in endometriosis research. *Fertil Steril* 2014;102:1213–22.
77. Miller LM, Johnson NP. EPHEct—the Endometriosis Phenome (and Biobanking) Harmonisation Project—may be very helpful for clinicians and the women they are treating. *F1000Res* 2017;6:14.
78. Vitonis AF, Vincent K, Rahmioglu N, et al. World Endometriosis Research Foundation Endometriosis Phenome and biobanking harmonization project: II. Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril* 2014;102:1223–32.
79. Surrey ES, Soliman AM, Johnson SJ, Davis M, Castelli-Haley J, Snabes MC. Risk of developing comorbidities among women with endometriosis: a retrospective matched cohort study. *J Womens Health (Larchmt)* 2018;27:1114–23.
80. Greco CD. Management of adolescent chronic pelvic pain from endometriosis: a pain center perspective. *J Pediatr Adolesc Gynecol* 2003;16(3 Suppl):S17–9.
81. Jarrell JF, Vilos GA, Allaire C, et al. Consensus guidelines for the management of chronic pelvic pain. *J Obstet Gynaecol Can* 2005;27:781–826.
82. Rubi-Klein K, Kucera-Sliutz E, Nissel H, et al. Is acupuncture in addition to conventional medicine effective as pain treatment for endometriosis? A randomised controlled cross-over trial. *Eur J Obstet Gynecol Reprod Biol* 2010;153:90–3.
83. Wayne PM, Kerr CE, Schnyer RN, et al. Japanese-style acupuncture for endometriosis-related pelvic pain in adolescents and young women: results of a randomized sham-controlled trial. *J Pediatr Adolesc Gynecol* 2008;21:247–57.
84. Goncalves AV, Barros NF, Bahamondes L. The practice of Hatha yoga for the treatment of pain associated with endometriosis. *J Altern Complement Med* 2017;23:45–52.
85. Meissner K, Schweizer-Arau A, Limmer A, et al. Psychotherapy with somatosensory stimulation for endometriosis-associated pain. *Obstet Gynecol* 2016;128:1134–42.
86. 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.
87. Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstet Gynecol* 2008;111:1285–92.
88. Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004;82:878–84.
89. Rizk B, Fischer AS, Lotfy HA, et al. Recurrence of endometriosis after hysterectomy. *Facts Views Vis Obgyn* 2014;6:219–27.
90. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update* 2014;20:737–47.
91. Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ* 2017;356:j372.
92. Phung TK, Waltoft BL, Laursen TM, et al. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. *Dement Geriatr Cogn Disord* 2010;30:43–50.
93. Laughlin-Tommaso SK, Khan Z, Weaver AL, Smith CY, Rocca WA, Stewart EA. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. *Menopause* 2018;25:483–92.
94. Mann J, Shuster J, Moawad N. Attributes and barriers to care of pelvic pain in university women. *J Minim Invasive Gynecol* 2013;20:811–8.
95. Denny E. Women's experience of endometriosis. *J Adv Nurs* 2004;46:641–8.
96. Roomaney R, Kagee A. Salient aspects of quality of life among women diagnosed with

endometriosis: A qualitative study. *J Health Psychol* 2018;23:905–16.

97. Gilmour JA, Huntington A, Wilson HV. The impact of endometriosis on work and social participation. *Int J Nurs Pract* 2008;14:443–8.

98. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. *Am J Obstet Gynecol* 2008;198:34.e31–7.

99. Jacoby VL, Fujimoto VY, Giudice LC, Kuppermann M, Washington AE. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. *Am J Obstet Gynecol* 2010;202:514–21.

100. Allaire C, Williams C, Bodmer-Roy S, et al. Chronic pelvic pain in an interdisciplinary setting: 1-year prospective cohort. *Am J Obstet Gynecol* 2018;218:114.e1–12.

101. Vercellini P, Giudice LC, Evers JL, Abrao MS. Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal. *Hum Reprod* 2015;30:1996–2004.

102. Bedaiwy MA, Allaire C, Yong P, Alfaraj S. Medical management of endometriosis in patients with chronic pelvic pain. *Sem Reprod Med* 2017;35:38–53.