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Authors

Giudice, Linda C

Horne, Andrew W

Missmer, Stacey A

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Time for global health policy and research leaders to prioritize endometriosis

Linda C. Giudice, Andrew W. Horne & Stacey A. Missmer



Endometriosis is an incurable, under-diagnosed, systemic inflammatory disease affecting millions world-wide. Common symptoms include life-impacting pain, gastrointestinal/urinary symptoms, excessive fatigue, and infertility. Global public health policies are urgently needed to promote awareness, implement multi-disciplinary care, and fund research for aetiology, biomarker discovery, and effective therapies for symptoms associated with endometriosis.

Patient and public health impact of underinvestment in endometriosis

Defined by endometrium (uterine lining)-like tissue outside the uterus, endometriosis is a little known, common, hormone-dependent, inflammatory disorder currently diagnosed by surgical or radiologic visualisation of disease¹. While mainly associated with life-impacting pelvic pain, painful menstruation and sexual intercourse, infertility, fatigue, and depression, those affected also have higher risk of non-reproductive sequelae, including high blood pressure, cardiovascular disease, autoimmune conditions, gastrointestinal and urologic symptoms, multifocal pain, migraines, and ovarian and breast cancer¹ (Fig. 1). Endometriosis affects ~10% of persons with a uterus, commonly striking teens and persisting across the reproductive life span (and sometimes beyond), greatly impacting personal relationships, educational and employment opportunities, and quality of life^{2,3}. Risk of developing disease is ~50% genetic, with no specific “endometriosis gene” or consistently identified environmental triggers¹.

Reliance on surgery and marginal advances in medical therapies for symptom relief maintain delayed diagnosis and insufficient care for many¹. Moreover, menstrual stigma, pain in women, sexism, and racism are impediments globally for life-improving care^{3,4}. Lack of awareness and/or discomfort regarding menstrual health remains surprisingly prevalent among healthcare providers^{3,4}.

Clinical specialties are commonly siloed, which diminishes recognizing and addressing endometriosis in clinical practices and specialist care outside gynecology^{1,3}. Siloed structures also negatively impact awareness and applying cutting-edge technologies to multi-disciplinary scientific discovery of causes, diagnostics, and treatments for endometriosis³⁻⁵. Impediments to determining aetiology and pathophysiology, classifying clinically-relevant subphenotypes, diagnosing, and treating endometriosis include socio-cultural factors that continue its obscurity among practitioners and the public^{1,3,4}. Here we

summarize challenges in endometriosis care and advancing research in this space.

A primary hypothesis for pelvic endometriosis establishment is through transplantation of endometrial tissue refluxed through the oviducts during menses, attaching to and invading pelvic organs, and eliciting a profound inflammatory response and fibrosis¹. This is replicated in experimental rodent models that utilize seeding with heterologous or homologous endometriotic tissue⁷. However, this paradigm is insufficient, as nearly all persons with uteri experience “retrograde menstruation” and rodents do not menstruate. Thus genetic, epigenetic, hormonal, immunologic factors, endometrial stem cells, and coelomic metaplasia, have been implicated in establishment/survival of lesions (with pathway-informative somatic mutations)—complementing the theory that retrograde menstruation plays a causal role^{1,4}. While mechanisms underlying this complex pathophysiology are slowly being elucidated, a comprehensive understanding of disease origins is wanting. This has stalled comprehensive animal models with disease fidelity—hampering research on endometriosis overall⁶.

Mechanisms underlying endometriosis-associated pain are complex⁷. Key to establishing lesions and activating peripheral pain pathways are new blood vessels and nerve sprouting (neuroangiogenesis)⁷. Also, in the central nervous system, brain volume and regional biochemical alterations accompany chronic endometriosis-related pain⁷. Endometriosis is also associated with infertility—attributed to scarred Fallopian tubes, diminished egg quality, and/or disrupted hormone signaling within the uterus^{1,3,4}. Improved understanding of endometriosis pathogenesis and its complex and heterogeneous manifestations and physiologic impacts are essential to develop improved diagnostics and patient-centred therapies.

Heterogeneous presentation of endometriosis impedes diagnosis and treatment

Most pelvic endometriosis comprises three subtypes: superficial peritoneal, ovarian cysts (“endometrioma”), and deep disease¹. Symptom manifestation and severity vary, and underdiagnosis is common due to erroneous symptom normalization and overlap with other diseases⁸. Recently, refined imaging techniques identify, with high accuracy, ovarian and deep disease, but reliance on surgical visualisation for the most common superficial peritoneal lesions continues to impede timely diagnosis^{3,4}. Surgery or imaging requires access to healthcare services, which varies significantly across socioeconomic and racial/ethnically underserved groups and geographies^{4,9}. Average diagnostic delay is 7 years after symptom onset, with delays >10 years not uncommon^{4,9}. There remains no reliable non-invasive biomarker of any endometriosis subtype⁴.

Treatment of pain symptoms falls broadly into surgical removal of disease and associated adhesions and hormonal suppressive therapies,

Action is needed to improve diagnosis of and care for people with endometriosis

Affects roughly 10% (190 million) girls, women, and trans men globally

- Associated with severe, life-impacting pain, fatigue, and sometimes depression, anxiety and infertility
- Most experience barriers to diagnosis resulting in delay of care for many years

Millions of lives would be improved with

- Resources to support fundamental research for disease cause(s), biomarker and treatment discovery, and potentially prevention or cure
- Improved medical education regarding menstrual health and signs and symptoms of endometriosis across specialities and in schools
- Standardised delivery of multidisciplinary care that evolves with patient symptoms and priorities across the life-course



Fig. 1 | Endometriosis is a global disease needing global solutions. Basic research is key to understanding its causes and molecular and genomic underpinnings, leading to novel diagnostics and therapeutics to alleviate symptoms and ultimately discover a cure. Education of professional and lay communities and leaders

throughout the world about endometriosis and its intersection with social determinants of health are key components to improve the lives of those affected. Moreover, multidisciplinary care is essential for holistic management of this complex and multi-dimensional disorder.

including combined oral contraceptive steroids, progestins, gonadotropin releasing hormone analogues, androgens and aromatase inhibitors¹⁰. Medical therapies that decrease oestrogen (or counter oestrogen action) are prescribed, because steroids play a key role in the pathophysiology of endometriosis¹. Unfortunately, both approaches are suboptimal. Surgery is associated with recurrence rates up to 50% within 5 years, and contraceptive hormone treatments often have unacceptable side effects and are counterproductive to fertility goals¹⁰. Geographic and financial barriers to accessing treatment from endometriosis-trained healthcare providers are common⁹. Surveys of patients consistently highlight symptom relief and improved medical therapies that do not limit fertility as a top priority for research³. Historically, pharmaceutical companies were reluctant to develop new drugs for endometriosis, and focus has been on variations of hormonal, anti-inflammatory, or repurposed therapies¹¹, lacking revolutionary impact. While novel treatment discovery is essential, clinical trials for endometriosis have been plagued by widespread variations in outcome reporting, and only a fraction of completed trials is published¹¹.

Emerging chronic pelvic pain-focused therapies that include considerations of neuropathic and nociceptive pathways have not been adequately studied¹². Those with persistent/recurrent pain have a high rate of hysterectomy¹² which does not eliminate pain recurrence and may heighten risks for multiple conditions later in life¹⁰. Further, commonly reported life-impacting concerns including fatigue and impaired sexual functioning have yet to be targeted for treatment among patients with endometriosis. A critical impediment to discovery of novel diagnostics and treatments and personalized approaches is the lack of a prognostically correlated classification of the highly heterogeneous presentation of endometriosis lesion types and symptoms, which includes variation and evolution within patients across the life-course^{3,4}.

Endometriosis funding landscape and the socioeconomic cost of underinvestment

The first economic study (2011) revealed the average cost of endometriosis was ~€9579/woman/year (€6298 lost work-productivity, €3113 direct health care costs)—similar to diabetes, Crohn's disease, and rheumatoid arthritis¹³. However, unlike these well-known diseases with similar socioeconomic impact and burden but considerably lower prevalence in the general population, there is relatively little investment in research into causes and disease mechanisms of endometriosis⁵. Recent governmental attention has included an increase in NIH funding for endometriosis research to \$16 M (0.04% of the total NIH budget) for the year 2022 (\$2/person with endometriosis/year), while Crohn's disease received \$90 M (\$130/person with Crohn's/year)¹⁴. Data consistently demonstrate that female-specific conditions are disproportionately underfunded⁵. Further, female reproductive conditions are largely absent from open access reference databases on which much of advanced biomolecular data science relies (e.g., ENCODE, NIH Roadmap epigenomics, GTEx, TissueNexus), impeding novel discovery, although recent endometrium and endometriosis single-cell transcriptomic data should soon appear in the Human Cell Atlas⁴.

Commitments to endometriosis research and care and moving forward

Despite identification of endometriosis as a chronic inflammatory pain condition with multi-systemic symptoms and co-morbidities^{1,8}, as a disease associated with menstruation and pelvic pain, it is still generally considered a gynaecologic disorder. This reductive concept has resulted in lowered healthcare system and research prioritization, limited integration, and impeded translation of rapidly developing scientific, multi-omic, genetic, bioengineering, and clinical discoveries in pain and inflammation. Their application would hasten identifying

shared and unique features of endometriosis, leading to novel therapeutics and multi-disciplinary approaches to symptom management.

Essential to improving diagnosis and care for endometriosis patients is ensuring they are heard and believed when expressing their symptoms to themselves, their personal support networks, and especially to healthcare providers^{4,10}. The 2021 WHO Endometriosis Fact Sheet (<https://www.who.int/news-room/fact-sheets/detail/endometriosis>) is a welcome leap forward to increase awareness globally. We posit that education and improved awareness including menstrual wellbeing curricula within schools for students of all gender identities could overcome menstruation taboos, ensure understanding of a 'normal' period, and when to seek help for distressing symptoms. Improved medical education regarding menstruation and endometriosis signs and symptoms could be ensured with thoughtful targets, e.g., including questions about menstrual health and non-malignant gynaecologic conditions on medical training board examinations, and larger scale initiatives such as revision of didactic teaching and medical curricula to prioritize menstrual health as critical to patient care.

Once diagnosed, individuals with endometriosis require personalised, multimodal, interdisciplinary treatment across the life-course to meet challenges of the evolving disease and changing patient priorities. First proposed in 2006, this novel care approach is optimally delivered through specialist centres comprised of integrated services including gynaecologists, endometriosis specialist nurses, and experts in imaging, pain medicine, psychology, physiotherapy, fertility, colorectal surgery, urology, and gastroenterology¹⁵. Whilst specialist centres have been successfully implemented in the UK and a few European countries (e.g., Denmark, Germany, France), this is not standard of care worldwide. Importantly, care delivery models incorporating mobile and digital technologies, and including primary care providers, specialists, pharmacy-based, community-based, and risk-prevention approaches, offer great opportunities and need development and investment⁴. For example, the Australian National Action Plan for Endometriosis launched in 2018 with \$58 M additional funding in 2022 supports a 4-year plan to fund research and establish specialist endometriosis and pelvic pain clinics in every state and territory. Restructuring similar models globally could fulfil personalized care in all regions.

As delayed or undiagnosed endometriosis leads to compromised health, promoting awareness, improving access to care, and implementing multidisciplinary care paradigms are urgently needed in global public health policies. Equally urgent and important are prioritizing and committing resources to support fundamental research and biomarker discovery to shorten the protracted time to diagnosis and provide effective, long-term therapies for this chronic and debilitating disorder to the benefit of millions world-wide.

Linda C. Giudice ¹✉, Andrew W. Horne ² & Stacey A. Missmer ^{3,4}

¹Distinguished Professor, Center for Reproductive Sciences, Center for Reproductive Health, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA. ²Professor of Gynaecology and Reproductive Sciences, EXPPECT Edinburgh and Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK. ³Professor of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, Grand Rapids, MI, USA. ⁴Adjunct Professor of Epidemiology, Harvard

T.H. Chan School of Public Health, Boston, MA, USA.

✉ e-mail: Linda.Giudice@ucsf.edu

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Author contributions

L.C.G. conceived the topic and wrote the initial draft, which was extensively revised with A.W.H. and S.A.M.. L.C.G. contributed much of the scientific information about endometriosis pathogenesis and pathophysiology. A.W.H. contributed key concepts about public health relevance and endometriosis clinical symptoms, clinical care, and health disparities. S.A.M. contributed key concepts in the epidemiology of endometriosis, status of funding for research and multi-disciplinary care models. L.C.G., A.W.H., and S.A.M. each provided references throughout the manuscript and in areas of their expertise and assured accuracy of citations and worked as a team on revising the manuscript resulting in its final form.

Competing interests

L.C.G. is funded by the National Institutes of Health P01 HD106414, "UCSF Stanford Endometriosis Center for Discovery, Innovation, Training and Community Engagement". She is co-author of patent filed by the Regents of the University of California, San Francisco, U.S. Application Serial No. 63/149,022, "Endometriosis-Related Methods and Compositions". She is past-President of the World Endometriosis Society and the American Society for Reproductive Medicine, and is a consultant for Celmatix, Myovant Sciences, and Gesynta Pharma. AH's institution (University of Edinburgh) has received payment for consultancy and grant funding from Roche Diagnostics to assist in the early development of a possible blood diagnostic biomarker for endometriosis. A.W.H.'s institution has received payment for consultancy fees from Gesynta and Jovi. A.W.H. has received payment for a presentation from Theramex. A.W.H.'s institution has received grant funding from the MRC, NIHR, CSO and Wellbeing of Women for endometriosis research. A.W.H. is listed as a co-inventor on a UK Patent Application (No. 2217921.2). A.W.H. is President-elect of the World Endometriosis Society and co-Editor in chief of *Reproduction and Fertility*. AH has been a member of the NICE and ESHRE Endometriosis Guideline Groups. AH is a Trustee and Medical Advisor to

Endometriosis UK. S.A.M. receives research support from National Institutes of Health, USA Department of Defense, AbbVie, and Marriott Family Foundations. She is President of the World Endometriosis Society, the Field Chief Editor for *Frontiers in Reproductive Health* and has served on advisory boards for AbbVie, Roche, and Abbott.

Additional information

Correspondence and requests for materials should be addressed to Linda C. Giudice.

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