frontiers | Frontiers in Global Women's Health

PERSPECTIVE
published: 10 May 2022
doi: 10.3389/fgwh.2022.902371

Endometriosis Is Undervalued: A Call to Action

Katherine Ellis[1], *Deborah Munro*[1*] *and Jennifer Clarke*[2]

[1] *Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand,* [2] *Faculty of Health, University of Canterbury, Christchurch, New Zealand*

Endometriosis is an inflammatory chronic pain condition caused by uterine tissue growing outside of the uterus that afflicts at least 11% of women (and people assigned female at birth) worldwide. This condition results in a substantial burden to these women, and society at large. Although endometriosis was first identified over 160 years ago, substantial knowledge gaps remain, including confirmation of the disease's etiology. Research funding for endometriosis is limited, with funding from bodies like the National Institutes of Health (NIH) constituting only 0.038% of the 2022 health budget—for a condition that affects 6.5 million women in the US alone and over 190 million worldwide. A major issue is that diagnosis of endometriosis is frequently delayed because surgery is required to histologically confirm the diagnosis. This delay increases symptom intensity, the risk of central and peripheral sensitization and the costs of the disease for the patient and their nation. Current conservative treatments of presumed endometriosis are pain management and birth control. Both of these methods are flawed and can be entirely ineffective for the reduction of patient suffering or improving ability to work, and neither addresses the severe infertility issues or higher risk of certain cancers. Endometriosis research deserves the funding and attention that befits a disease with its substantial prevalence, effects, and economic costs. This funding could improve patient outcomes by introducing less invasive and more timely methods for diagnosis and treatment, including options such as novel biomarkers, nanomedicine, and microbiome alterations.

Keywords: endometriosis, funding, women's health, quality of life, chronic pain

OPEN ACCESS

Edited by:
Lysia Demetriou,
University of Oxford, United Kingdom

Reviewed by:
Pooja Popli,
Baylor College of Medicine, United States
Iris Brandes,
Hannover Medical School, Germany

***Correspondence:**
Deborah Munro
debbie.munro@canterbury.ac.nz

Specialty section:
This article was submitted to Quality of Life, a section of the journal Frontiers in Global Women's Health

Received: *23 March 2022*
Accepted: *19 April 2022*
Published: *10 May 2022*

Citation:
Ellis K, Munro D and Clarke J (2022) Endometriosis Is Undervalued: A Call to Action. Front. Glob. Womens Health 3:902371. doi: 10.3389/fgwh.2022.902371

INTRODUCTION

Endometriosis is a chronic inflammatory disease (1) that causes significant morbidity (2), and affects 10–15% of women of reproductive age globally (3–5). Conservatively, 1 in 9 women of reproductive age has endometriosis in the United States (US) (6) and Australia (7). Endometriosis causes tissue from the uterus to migrate and implant in other regions of the body (8, 9). This tissue interacts with the body's endocrine, musculoskeletal, vascular, reproductive, and nervous systems (10) causing numerous painful symptoms and physiological changes. There are three key types of endometriosis: superficial peritoneal, ovarian, and deep infiltrating (11). While peritoneal is the predominant presentation of the disease, ovarian affects 17–44% of endometriosis patients (12) and is characterized by the development of ovarian endometriomas, cystic lesions filled with dark endometrial fluid (13). Deep infiltrating endometriosis affects ∼20% of endometriosis patients (14) and is considered the most severe form (15). Each endometriosis subtype is thought to have a different pathogenesis (16), but no etiology is confirmed (17) that explains all disease manifestations (18).

SYMPTOM BURDEN

Symptoms

Misplaced endometriotic tissue causes a wide range of symptoms, including chronic pelvic pain, dysmenorrhea (menstrual pain), dyspareunia (painful sex), dysuria (painful urination), dyschezia (painful defecation) (19), metrorrhagia (mid-cycle bleeding), diarrhea, constipation, infertility (20), and myofascial pain, among others (1). Furthermore, the gastrointestinal symptoms of endometriosis patients are more severe than those of controls (21), which often results in both coexistence and misdiagnosis of irritable bowel syndrome (22). As the disease progresses, patients risk developing adhesions, fibrous scar tissue bands that can abnormally bind pelvic and abdominal organs (9). Endometriosis is the most frequent cause of adhesions in women and common areas for endometriosis adhesions include the anterior abdominal wall, bladder, and uterus (23). Adhesions can cause anatomical distortion, which can hinder fertility, cause rectal constriction, and be a cause of dyspareunia. In a 2019 study, the presence of endometriosis-associated adhesions was shown to significantly negatively impact quality of life (23).

The cumulative effect of these chronic pain symptoms is a substantial burden on sufferers (20) and 70% of patients live with unresolved pain (2), with impacts to all aspects of their quality of life (24). Research shows that endometriosis patients also have significantly higher rates of co-morbidities than control populations (25). The symptoms of endometriosis, particularly those associated with pain, increase the rates of chronic stress, anxiety, depression and decreased quality of life among endometriosis patients compared with those without the disease (26).

There is a well-established delay from symptom onset to diagnosis of 4–11 years for endometriosis patients (1). There are many reasons for this delay, including the lack of a unique symptom profile (27), the variety of symptoms (28) and large waitlists for the laparoscopies used to diagnose endometriosis (2). Many patients find it necessary to "doctor shop" to find a medical practitioner who will support their efforts to obtain an endometriosis diagnosis. In a 2004 study, 47% of endometriosis patients had seen at least five doctors before getting an endometriosis diagnosis or referral (29). This may be partially explained by the results of a 2021 French study, where 25% of general practitioners did not think they knew enough about endometriosis for their clinical practice (30). In a 2012 study of 173 endometriosis patients in Austria and Germany, 74.3% had experienced a misdiagnosis. These misdiagnoses included intolerances, appendicitis, irritable bowel syndrome, and pelvic inflammatory disease (31).

Pain

In addition to painful symptoms, patients can be subject to central and peripheral sensitization (10). Central sensitization is the abnormal processing of sensory signals (32) that results in exaggerated experiences of painful and non-painful stimuli (10) through enhanced pelvic nociception. Peripheral sensitization lowers the body's threshold for nociceptor activation with repetitive and prolonged stimulation, as occurs in endometriosis (10). The combined effect of these phenomena is that over time non-painful stimuli can produce incredibly painful signals in sensitized patients.

Women with chronic pelvic pain, with or without a confirmed diagnosis, show significantly lower pain tolerances than controls (33). The severity of the decrease in pain tolerance corresponds to the duration of symptoms (33) supporting the theory that delayed diagnosis increases patient sensitization. An Australian study found endometriosis patients have significantly higher functional pain disability (pain interference with daily activities like sleep, relationships and work) than women without endometriosis (34). Furthermore, women have higher pain sensitivity than men (35, 36) as a result of complex interactions in women of anatomical, hormonal, physiological, and psychological factors (37).

Cancer Associations

Endometriosis is a non-neoplastic invasive disease (38), although there is evidence to suggest a positive association between endometriosis and ovarian cancer (39). There is molecular evidence to suggest endometriotic lesions can undergo a transformation to clear cell and endometrioid ovarian cancers (40). This connection is controversial, and like many aspects of endometriosis, requires much more study to fully outline the potential mechanisms involved. The indication is that endometriosis increases ovarian cancer risk (19) from 1.3% in the general female population to 1.8% of endometriosis patients (41).

Infertility

In addition to the extensive pain symptoms endometriosis patients experience, endometriosis patients have a high prevalence of infertility and sub-fertility among their cohort. Half of endometriosis patients suffer from fertility issues (42), and up to half of women with unexplained infertility or sub-fertility are subsequently found to have endometriosis (43, 44). The high rates of endometriosis interfering with fertility may relate to factors including anatomical distortions (45), diminished ovarian reserve, chronic inflammation and compromised endometrial receptivity (42).

LACK OF FUNDING

Endometriosis is a condition that impacts not only patients, but their families, jobs, societies, and countries. The authors believe the present issues with diagnosing, treating and funding endometriosis result from many years of misunderstanding and ignoring important female health topics. Improving funding for endometriosis research could improve the understanding of the condition, eliminate knowledge gaps, reduce time to diagnosis, expand available treatment options, improve pain management and place a long-overdue emphasis on predominantly female experiences of illness.

The National Institutes of Health (NIH) is the largest source of biomedical research funding globally, allocating $41.7 billion USD annually (46). In 2022, the expected funding allocation for endometriosis is $16 million (47), 0.038% of the budget. Since the conservative estimate is that endometriosis affects 11% of US women in their lifetime, only $2.00 per patient per year is

allocated. As a comparison, 12% of US women are expected to suffer from diabetes in their lifetime (48). If it is assumed that half of the allocated diabetes research budget was for female sufferers, there is a funding allocation of $31.30 per woman, over 1,500% more than for endometriosis.

Crohn's disease, like endometriosis, is a chronic inflammatory condition (49). Crohn's disease affects the digestive tract lining, resulting in abdominal pain, weight loss, diarrhea, and fatigue (50). There are over 690,000 people with Crohn's disease in the US, or 0.21% of the population (51). In 2022, Crohn's disease research will receive $90 million in funding, $130.07 per patient, over 65 times more per patient than for endometriosis. This comparison is not to suggest Crohn's disease is overfunded, but that endometriosis is seriously underfunded.

ECONOMIC BURDEN OF ENDOMETRIOSIS

The burden of endometriosis on individual patients is substantial (20) both before and after diagnosis (52). The impact of ongoing pain can cause some patients to lose their jobs or their partners (53). Additionally, the financial burden is significant. Endometriosis patients have significantly higher healthcare resource utilization, and direct and indirect healthcare costs than controls. Endometriosis patients in the US spend $26,305 USD more than controls on healthcare expenses in the 5 years before and after diagnosis (52). In the year after diagnosis patients with endometriosis spend on average 3.5 times the amount on healthcare than controls do (25). The direct costs of endometriosis include in and outpatient treatment, surgery, and prescription costs, which in the US average $12,118 per patient, per year (54). Indirect costs, including days of work lost and reduced quality of work, were almost $16,000 per patient per year (54). In a study across ten countries lost productivity costs were generally double those of healthcare costs (55) as the average patient loses 6.4 h of work a week to presenteeism (reduced effectiveness while working) (56). Endometriosis patients begin to suffer from their condition at a young age, during a very productive period of their lives. The additive effects of fatigue, productivity loss, and time removed from the workforce, schooling and training create an immense barrier to patients being able to effectively progress in life, take up career opportunities, and in their capacity to save their earnings.

The total US endometriosis economic burden is estimated to be as high as $78–119 billion annually (54, 57). In Australia, the annual cost of endometriosis was estimated to be $16,970–20,898 per woman, per year, with 75–84% of the total due to productivity losses (58). Delays until endometriosis diagnosis increase not only the number of pre-diagnosis endometriosis symptoms but also emergency visits, hospitalizations, and overall healthcare costs (59). Compared to short delays of less than a year, long delays of 3–5 years from first symptom presentation to diagnosis, increased the cost of healthcare in the 5 years prior to diagnosis by $12,971–34,460 (59).

Lost workdays are also higher among endometriosis patients than control populations (25). In Australia, where the annual economic burden of endometriosis is estimated to be $6.5 (58) to $7.4 billion (60), endometriosis patients used on average 60% of their sick leave to treat their chronic pain (60). In a 2022 study, 65% of an Australian cohort of endometriosis patients used unpaid leave to manage their endometriosis symptoms, 64% felt judged in the workplace for their symptoms, and one in seven reported being fired as a result of their condition (61).

Furthermore, research shows there are immense productivity losses due to endometriosis for women in the workforce, even while at work. Fatigue is more common among endometriosis patients, than in control populations (62). In a 2021 Canadian study on fatigue, endometriosis patients reported substantial impairments to their work productivity with 46.5% overall work impairment due to endometriosis-related symptoms (63). These findings were like a 2013 Danish study that found that patients with endometriosis had significantly more pain than controls, were in more pain when using their sick days and used more sick days (64). This study also found that many women were embarrassed by their symptoms, felt obligated to use their sick days and often felt unable or too tired to do a satisfying job (64).

In the US, the diabetes economic burden is $327 billion (65), and with 37.3 million Americans with diabetes (48), that accounts for $8,767 of burden per patient. By comparison, the estimated economic burden of endometriosis in the US would account for $9,754–14,881 per patient, 11–70% higher than for diabetes. Thus, it is evident to the authors there is an immense financial burden not only on endometriosis patients but on nations with patients who then require high levels of healthcare utilization. These patients frequently cannot participate in their workplaces and economies to the degree they wish because of symptoms, incurring a further cost to patients and society. If endometriosis was funded by the NIH at the same level as diabetes with respect to the annual economic burden, endometriosis funding would need to increase to $298.8–455.3 million, rather than the current $16 million.

THE PRESENT OPTIONS

Low research funding for endometriosis research means knowledge gaps are not being filled, making the development of effective diagnosis and treatment options more complicated, more time consuming, and less enticing for researchers. As a consequence, presently available options to treat endometriosis are severely limited. There are also high recurrence rates of symptoms and disease for current interventions (66). Recurrence of symptoms for non-surgical therapies, such as birth control and pain management, are rapid (18), because non-surgical treatments reduce or repress symptoms, but do not cure the disease. Furthermore, these methods are entirely inefficacious for endometriosis-associated fertility issues (19). Effective, non-invasive, non-hormonal treatments are required but are not currently available to the over 190 million global endometriosis patients (67).

Birth Control

Birth control is a standard endometriosis treatment (68). Endometriosis birth control methods include intrauterine progesterone devices, progestin injections and combined

hormone pills (69). Combined treatments increase the risk of thromboembolism, nausea and breast tenderness. Progestin injections can cause weight gain, decreased bone density, worsened acne, and depression (69). Birth control is also a limited treatment for endometriosis, as many women cannot use birth control because the side effects are too severe or because of a desire to get pregnant.

Pain Management

Pain is the most common symptom of endometriosis (70). However, endometriosis pain management is complex. There is inconclusive evidence that non-steroidal anti-inflammatory drugs provide greater relief than placebos (71). Opioids are not a recommended treatment for endometriosis (72); however, in a cohort of 113,506 endometriosis patients in the US, 89% were utilizing opioids to manage their pain (25). Chronic opioid use can significantly increase healthcare costs for endometriosis patients compared to non-chronic users (73). Long-term opioid use for non-cancerous chronic pain, such as endometriosis, is controversial and results in an absolute adverse event rate of 78% (74). The high use of opioids among this cohort is indicative of the intensity of the pain experienced, but this approach can lead to addiction and side effects, including constipation, nausea, confusion and drowsiness (75). The required dosage to manage pain also increases with chronic use as the body becomes habituated to it (76).

Surgery

Laparoscopic surgery is considered the "gold-standard" for diagnosing and treating endometriosis (18) and is the only method available to "confirm" endometriosis histologically (77) which provides a clear and unambiguous diagnosis for patients that is often essential for practitioners to provide the best treatment plan. According to one study, 42% of patients have undergone at least three surgeries (2). Surgery is thus an impermanent solution for many patients, with recurrence of both symptoms and lesions (19) expected for 40–50% of patients within 5 years (78), and this repeated intervention can exacerbate pain and fertility issues (79). Furthermore, surgery is a trauma to the body that activates adrenergic signaling, suppresses cell-mediated immunity and promotes angiogenesis (80). In mice with induced endometriosis, subsequent surgery increased lesion weight and microvessel density (80), which is counteractive to the intent of surgery for endometriosis.

EVOLVING POSSIBILITIES

Earliest descriptions of endometriosis date back to 1860 (81) and 1920 (82). However, we still do not understand its etiology (70), the biology and function of both healthy female and endometriotic peritoneum, or the actions of endometrial stem cells (83). A substantial amount of knowledge still needs to be collected, collated, and applied to patient care. The lack of progress despite the relatively high volume of papers published about endometriosis indicates the complexity of endometriosis and the limited global funding available (83). Despite these issues, endometriosis research has been undertaken by talented researchers, and there are many promising avenues for further endometriosis research.

New Biomarker Analysis

One of the key aspects impacting the diagnosis and treatment of endometriosis is the lack of non-invasive diagnostic tools. Biomarkers present an appealing option for non-invasive diagnosis of endometriosis. However, many biomarkers that have been assessed previously could only discern advanced disease, indicating a need for more research to locate biomarkers that can diagnose "milder" cases of the disease (84). In a 2021 study, the researchers found patients with endometriosis had distinct microbial communities in their peritoneal fluid and feces compared to the control group. In the peritoneal fluid of endometriosis patients, there were more pathogens, while there was a loss of protective microbes in feces samples (85). The authors concluded that *Ruminococcus* in the gut and *Pseudomonas* in the peritoneal fluid may be able to act as auxiliary diagnostic tools for endometriosis with further investigation into the interactions of micro-organisms and endometriosis required (85).

Follicular fluid can be obtained from follicles by fine-needle aspiration following oocyte removal (5). Researchers have found endometriosis patients have dysregulated cytokine profiles in their follicular fluid with significant upregulation of IL-1β and IL-6 (86). Conversely, the concentration of IL-12, an anti-inflammatory cytokine, inflammatory cytokine IL-10 and E-cadherin levels were lower among endometriosis patients compared to controls (5). In a 2021 study, the measurement of IL-10 in follicular fluid was able to perfectly differentiate between endometriosis patients and controls (5).

Nanomedicines

One technology in its infancy for the treatment of endometriosis is the use of nanoparticles to aid in the imaging of, directly treating or delivering drugs to treat endometriosis (87). The key limitation for this emerging technology is that the etiology and pathogenesis of endometriosis are unknown (87). Despite this, investment in nanomedicines for endometriosis could substantially augment the capacity to diagnose and treat endometriosis. Nanoparticles have shown a capacity to accumulate in endometriotic lesions (87), which could improve the use of imaging technologies to diagnose endometriosis. This technology could also provide a method for targeting endometriotic lesions without the requirement of surgery. Potential drugs that could be delivered by nanotechnological methods could be anti-inflammatory, antioxidant, anti-angiogenic and immunomodulating molecules (88), which may have the capacity to reduce the size of or eliminate endometriosis lesions, rather than just suppress symptoms. However, much more pre-clinical and clinical research is required to support the use of this emerging technology for endometriosis (88).

Alterations to the Microbiome

Imbalances to gut microbiota composition have been connected to the compromised immunosurveillance and altered immune

profiles associated with endometriosis (89), with animal studies consistently showing the impact of the gut microbiota on endometriosis and endometriosis on gut microbiota (90). In addition to being a potential site for novel biomarkers, the gut microbiota may be a target site for new treatments. In a 2019 study by Chadchan et al., mice with induced endometriosis were subjected to antibiotic therapies (91). Broad-spectrum antibiotics were shown to significantly reduce lesion size and inflammatory response. Furthermore, the authors showed that fecal transfer from mice with endometriosis restored lesion growth and inflammation in mice treated with the antibiotic metronidazole (91). Conversely, metronidazole-treated mice that received fecal transfers from mice without endometriosis had significantly smaller lesions, suggesting a role for the gut microbiome in the progression of endometriosis (91). The effect of gut microbiota on endometriosis is not solely negative. The bacteria-derived metabolite n-butyrate is a short-chain fatty acid that is significantly downregulated in mice with induced endometriosis. In a 2021 study, n-butyrate treatment significantly reduced lesion growth and inflammatory cell infiltration in a mouse model (92). Therapies that address endometriotic alterations to the gut microbiota could have immense potential to reduce the growth of lesions and the effects of inflammation for endometriosis patients.

DISCUSSION

Despite progress, critical gaps remain in the fundamental understanding of endometriosis. This means there are opportunities to substantially expand and improve our core understanding of this important health topic. The authors feel endometriosis warrants more attention to fill these fundamental knowledge gaps. There are not enough people working in this vital space, likely due to insufficient funding. If endometriosis was funded by the NIH at half the level of diabetes, the budget would increase almost 16 times to over $250.4 million annually. It is the belief of the authors that present levels of endometriosis funding do not reflect the immense pain of patients, long delays in diagnosis, the ineffectiveness of common treatment options, massive knowledge gaps, substantial economic burdens or the immense costs borne by individual patients. Unexplored in the scope of this paper, but vital, is the investment into structures to translate research findings into clinical care, understanding of the epidemiological underpinnings of patient diversity, increased awareness through public education about endometriosis so affected patients are better aware, and into healthcare practitioner training about how best to treat and support endometriosis patients.

There is a lot of promising research underway that could create substantial positive ramifications for patients. These include the chance for non-invasive biomarker auxiliary diagnosis methods, the application of nanoparticle drug delivery and treatments targeting the microbiome. An area of immense potential for developing new non-invasive diagnostic and treatment options may be the application of nanoparticles to deliver therapies directly to endometriotic lesions.

Advancement in the identification and treatment of endometriosis is challenging but entirely possible. It is the opinion of these authors that if endometriosis had more representative funding, the rate of advancement of non-invasive diagnostic and treatment methods could be significantly increased, with long-term benefits for patients and society.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KE is the first author of this paper through conception and literature collection. DM and JC have contributed equally to this work by critically revising and editing the article. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Biomolecular Interaction Centre (BIC) for their support and financial contribution to the Engineering Endometriosis Research Program at the University of Canterbury.

REFERENCES

1. Agarwal SK, Chapron C, Giudice LC, Laufer MR, Leyland N, Missmer SA, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol.* (2019) 220:354.e1–12. doi: 10.1016/j.ajog.2018.12.039
2. Agarwal SK, Foster WG, Groessl EJ. Rethinking endometriosis care: applying the chronic care model *via* a multidisciplinary program for the care of women with endometriosis. *Int J Womens Health.* (2019) 11:405–10. doi: 10.2147/IJWH.S207373
3. Mehedintu C, Plotogea MN, Ionescu S, Antonovici M. Endometriosis still a challenge. *J Med Life.* (2014) 7:349–57. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4233437/pdf/JMedLife-07-349.pdf
4. Buscemi S, Maiorana A, Fazzotta S, Incandela D, Palumbo VD, Damiano G, et al. Scar endometriosis: not a rare cause for a painful scar. *Clin Ter.* (2021) 172:129–33. doi: 10.7417/CT.2021.2299
5. Cela V, Malacarne E, Obino MER, Marzi I, Papini F, Vergine F, et al. Exploring epithelial-mesenchymal transition signals in endometriosis diagnosis and *In Vitro* fertilization outcomes. *Biomedicines.* (2021) 9:1681. doi: 10.3390/biomedicines9111681
6. Buck Louis GM, Hediger ML, Peterson CM, Croughan M, Sundaram R, Stanford J, et al. Incidence of endometriosis by study population and diagnostic method: the ENDO study. *Fertil Steril.* (2011) 96:360–5. doi: 10.1016/j.fertnstert.2011.05.087
7. Endometriosis in Australia: prevalence and hospitalisations. In: AIoHa W, editor. *Australian Institute of Health and Welfare (2019) Endometriosis in Australia: Prevalence and Hospitalisations.* Australian Government (2019).
8. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril.* (2012) 98:511–9. doi: 10.1016/j.fertnstert.2012.06.029
9. Tomassetti C, Johnson NP, Petrozza J, Abrao MS, Einarsson JI, Horne AW, et al. An international terminology for endometriosis, 2021.

Facts Views Vis Obgyn. (2021) 13:295–304. doi: 10.52054/FVVO.13.4.036
10. Aredo JV, Heyrana KJ, Karp BI, Shah JP, Stratton P. Relating chronic pelvic pain and endometriosis to signs of sensitization and myofascial pain and dysfunction. *Semin Reprod Med.* (2017) 35:88–97. doi: 10.1055/s-0036-1597123
11. Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Res.* (2019) 8:1–28. doi: 10.12688/f1000research.14817.1
12. Gałczyński K, Józwik M, Lewkowicz D, Semczuk-Sikora A, Semczuk A. Ovarian endometrioma – a possible finding in adolescent girls and young women: a mini-review. *J Ovarian Res.* (2019) 12:104. doi: 10.1186/s13048-019-0582-5
13. Hoyle A, Puckett Y. *Endometrioma*. Treasure Island, FL: StatPearls Publishing (2022). p. 2/1/22.
14. Laganà AS, Vitale SG, Trovato MA, Palmara VI, Rapisarda AMC, Granese R, et al. Full-thickness excision versus shaving by laparoscopy for intestinal deep infiltrating endometriosis: rationale and potential treatment options. *Biomed Res Int.* (2016) 2016:3617179. doi: 10.1155/2016/3617179
15. Cohen J, Mathieu d'Argent E, Selleret L, Antoine JM, Chabbert-Buffet N, Bendifallah S, et al. [Fertility and deep infiltrating endometriosis]. *Presse Med.* (2017) 46:1184–91. doi: 10.1016/j.lpm.2017.10.002
16. Young VJ, Ahmad SF, Duncan WC, Horne AW. The role of TGF-β in the pathophysiology of peritoneal endometriosis. *Hum Reprod Update.* (2017) 23:548–59. doi: 10.1093/humupd/dmx016
17. Streuli I, de Ziegler D, Santulli P, Marcellin L, Borghese B, Batteux F, et al. An update on the pharmacological management of endometriosis. *Expert Opin Pharmacother.* (2013) 14:291–305. doi: 10.1517/14656566.2013.767334
18. Falcone T, Flyckt R. Clinical management of endometriosis. *Obstet Gynecol.* (2018) 131:557–71. doi: 10.1097/AOG.0000000000002469
19. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol.* (2014) 10:261–75. doi: 10.1038/nrendo.2013.255
20. Fuldeore MJ, Soliman AM. Prevalence and symptomatic burden of diagnosed endometriosis in the United States: national estimates from a cross-sectional survey of 59,411 women. *Gynecol Obstet Invest.* (2017) 82:453–61. doi: 10.1159/000452660
21. Ek M, Roth B, Ekström P, Valentin L, Bengtsson M, Ohlsson B. Gastrointestinal symptoms among endometriosis patients–A case-cohort study. *BMC Womens Health.* (2015) 15:59. doi: 10.1186/s12905-015-0213-2
22. Chiaffarino F, Cipriani S, Ricci E, Mauri PA, Esposito G, Barretta M, et al. Endometriosis and irritable bowel syndrome: a systematic review and meta-analysis. *Arch Gynecol Obstet.* (2021) 303:17–25. doi: 10.1007/s00404-020-05797-8
23. Abd El-Kader AI, Gonied AS, Lotfy Mohamed M, Lotfy Mohamed S. Impact of endometriosis-related adhesions on quality of life among infertile women. *Int J Fertil Steril.* (2019) 13:72–6. doi: 10.22074/ijfs.2019.5572
24. Della Corte L, Di Filippo C, Gabrielli O, Reppuccia S, La Rosa VL, Ragusa R, et al. The burden of endometriosis on women's lifespan: a narrative overview on quality of life and psychosocial wellbeing. *Int J Environ Res Public Health.* (2020) 17:4683. doi: 10.3390/ijerph17134683
25. 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. doi: 10.1007/s12325-018-0667-3
26. Casalechi M, Vieira-Lopes M, Quessada MP, Arão TC, Reis FM. Endometriosis and related pelvic pain: association with stress, anxiety and depressive symptoms. *Minerva Obstet Gynecol.* (2021) 73:283–9. doi: 10.23736/S2724-606X.21.04704-3
27. Kiesel L, Sourouni M. Diagnosis of endometriosis in the 21st century. *Climacteric.* (2019) 22:296–302. doi: 10.1080/13697137.2019.1578743
28. Hudson N. The missed disease? Endometriosis as an example of 'undone science'. *Reprod Biomed Soc Online.* (2021) 14:20–7. doi: 10.1016/j.rbms.2021.07.003
29. Ballweg ML. Impact of endometriosis on women's health: comparative historical data show that the earlier the onset, the more severe the disease. *Best Pract Res Clin Obstet Gynaecol.* (2004) 18:201–18. doi: 10.1016/j.bpobgyn.2004.01.003
30. Roullier C, Sanguin S, Parent C, Lombart M, Sergent F, Foulon A. General practitioners and endometriosis: level of knowledge and the impact of training. *J Gynecol Obstet Hum Reprod.* (2021) 50:102227. doi: 10.1016/j.jogoh.2021.102227
31. Hudelist G, Fritzer N, Thomas A, Niehues C, Oppelt P, Haas D, et al. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Hum Reprod.* (2012) 27:3412–6. doi: 10.1093/humrep/des316
32. Hoffman D. Central and peripheral pain generators in women with chronic pelvic pain: patient centered assessment and treatment. *Curr Rheumatol Rev.* (2015) 11:146–66. doi: 10.2174/1573397111666150619094524
33. Grundström H, Gerdle B, Alehagen S, Berterö C, Arendt-Nielsen L, Kjølhede P. Reduced pain thresholds and signs of sensitization in women with persistent pelvic pain and suspected endometriosis. *Acta Obstet Gynecol Scand.* (2019) 98:327–36. doi: 10.1111/aogs.13508
34. Evans S, Mikocka-Walus A, Olive L, Seidman LC, Druitt M, Payne LA. Phenotypes of women with and without endometriosis and relationship with functional pain disability. *Pain Med.* (2020) 22:1511–21. doi: 10.1093/pm/pnaa362
35. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesthesia.* (2013) 111:52–8. doi: 10.1093/bja/aet127
36. Mogil JS, Bailey AL. Sex and gender differences in pain and analgesia. *Prog Brain Res.* (2010) 186:141–57. doi: 10.1016/B978-0-444-53630-3.00009-9
37. Pieretti S, Di Giannuario A, Di Giovannandrea R, Marzoli F, Piccaro G, Minosi P, et al. Gender differences in pain and its relief. *Ann Ist Super Sanita.* (2016) 52:184–9. doi: 10.4415/ANN_16_02_09
38. Zeitvogel A, Baumann R, Starzinski-Powitz A. Identification of an invasive, N-cadherin-expressing epithelial cell type in endometriosis using a new cell culture model. *Am J Pathol.* (2001) 159:1839–52. doi: 10.1016/S0002-9440(10)63030-1
39. Kvaskoff M, Mahamat-Saleh Y, Farland LV, Shigesi N, Terry KL, Harris HR, et al. Endometriosis and cancer: a systematic review and meta-analysis. *Hum Reprod Update.* (2021) 27:393–420. doi: 10.1093/humupd/dmaa045
40. Herreros-Villanueva M, Chen C-C, Tsai E-M, Er T-K. Endometriosis-associated ovarian cancer: what have we learned so far? *Clin Chim Acta.* (2019) 493:63–72. doi: 10.1016/j.cca.2019.02.016
41. Kvaskoff M, Horne AW, Missmer SA. Informing women with endometriosis about ovarian cancer risk. *Lancet.* (2017) 390:2433–4. doi: 10.1016/S0140-6736(17)33049-0
42. Marquardt RM, Kim TH, Shin JH, Jeong JW. Progesterone and estrogen signaling in the endometrium: what goes wrong in endometriosis? *Int J Mol Sci.* (2019) 20:3822. doi: 10.3390/ijms20153822
43. Jørgensen H, Hill AS, Beste MT, Kumar MP, Chiswick E, Fedorcsak P, et al. Peritoneal fluid cytokines related to endometriosis in patients evaluated for infertility. *Fertil Steril.* (2017) 107:1191–9.e2. doi: 10.1016/j.fertnstert.2017.03.013
44. Evans MB, Decherney AH. Fertility and Endometriosis. *Clin Obstet Gynecol.* (2017) 60:497–502. doi: 10.1097/GRF.0000000000000295
45. Olive DL, Pritts EA. The treatment of endometriosis: a review of the evidence. *Ann N Y Acad Sci.* (2002) 955:360-72; discussion 89-93:96–406. doi: 10.1111/j.1749-6632.2002.tb02797.x
46. NIH. Budget (2020). Available online at: https://www.nih.gov/about-nih/what-we-do/budget.
47. NIH. *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)*. Available online at: https://report.nih.gov/funding/categorical-spending#/2022.
48. CDC. National Diabetes Statistics Report (2020). Estimates of Diabetes and Its Burden in the United States. In: Services USDoHaH, editor. (2020).
49. Petagna L, Antonelli A, Ganini C, Bellato V, Campanelli M, Divizia A, et al. Pathophysiology of Crohn's disease inflammation and recurrence. *Biol Direct.* (2020) 15:23. doi: 10.1186/s13062-020-00280-5
50. Veauthier B, Hornecker JR. Crohn's disease: diagnosis and management. *Am Fam Physician.* (2018) 98:661–9. Available online at: https://www.aafp.org/afp/2018/1201/afp20181201p661.pdf
51. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. *Dis Mon.* (2018) 64:20–57. doi: 10.1016/j.disamonth.2017.07.001

52. 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. doi: 10.1016/j.fertnstert.2014.10.011
53. Halis G, Mechsner S, Ebert AD. The diagnosis and treatment of deep infiltrating endometriosis. *Dtsch Arztebl Int.* (2010) 107:446–56. doi: 10.3238/arztebl.2010.0446
54. 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. doi: 10.1093/humrep/dev335
55. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, 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. doi: 10.1093/humrep/des073
56. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, 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. doi: 10.1016/j.fertnstert.2011.05.090
57. D'Hooghe T, Dirksen CD, Dunselman GAJ, de Graaff A, Simoens S. The costs of endometriosis: it's the economy, stupid. *Fertil Steril.* (2012) 98:S218–S9. doi: 10.1016/j.fertnstert.2012.07.791
58. Armour M, Lawson K, Wood A, Smith CA, Abbott J. The cost of illness and economic burden of endometriosis and chronic pelvic pain in Australia: a national online survey. *PLoS ONE.* (2019) 14:e0223316. doi: 10.1371/journal.pone.0223316
59. Surrey E, Soliman AM, Trenz H, Blauer-Peterson C, Sluis A. Impact of Endometriosis diagnostic delays on healthcare resource utilization and costs. *Adv Ther.* (2020) 37:1087–99. doi: 10.1007/s12325-019-01215-x
60. Young E. The cost of endometriosis in Australia: A report for EndoActive by Ernst & Young. *EndoActive* (2019). Available online at: https://endoactive.org.au/wp-content/uploads/29May2019-FINAL-The-Cost-of-Endometriosis-in-Australia-EY-EndoActive-Report.pdf
61. Armour M, Ciccia D, Stoikos C, Wardle J. Endometriosis and the workplace: lessons from Australia's response to COVID-19. *Aust N Z J Obstet Gynaecol.* (2022) 62:164–7. doi: 10.1111/ajo.13458
62. Ramin-Wright A, Schwartz ASK, Geraedts K, Rauchfuss M, Wölfler MM, Haeberlin F, et al. Fatigue – a symptom in endometriosis. *Hum Reprod.* (2018) 33:1459–65. doi: 10.1093/humrep/dey115
63. Soliman AM, Rahal Y, Robert C, Defoy I, Nisbet P, Leyland N, et al. Impact of endometriosis on fatigue and productivity impairment in a cross-sectional survey of Canadian women. *J Obstet Gynaecol Can.* (2021) 43:10–8. doi: 10.1016/j.jogc.2020.06.022
64. Hansen KE, Kesmodel US, Baldursson EB, Schultz R, Forman A. The influence of endometriosis-related symptoms on work life and work ability: a study of Danish endometriosis patients in employment. *Eur J Obstet Gynecol Reprod Biol.* (2013) 169:331–9. doi: 10.1016/j.ejogrb.2013.03.008
65. Association AD. Economic costs of diabetes in the U.S. in. 2017. *Diabetes Care.* (2018). 41:917–28. doi: 10.2337/dci18-0007
66. Saunders PTK, Horne AW. Endometriosis: etiology, pathobiology, and therapeutic prospects. *Cell.* (2021) 184:2807–24. doi: 10.1016/j.cell.2021.04.041
67. Organisation WH. *Endometriosis.* (2021). Available online at: https://www.who.int/news-room/fact-sheets/detail/endometriosis#:~:text=Endometriosis%20affects%20roughly%2010%25%20(190,and%20girls%20globally%202) (accessed March 31, 2021).
68. Schrager S, Larson M, Carlson J, Ledford K, Ehrenthal DB. Beyond birth control: noncontraceptive benefits of hormonal methods and their key role in the general medical care of women. *J Womens Health.* (2020) 29:937–43. doi: 10.1089/jwh.2019.7731
69. Robbins CL, Ott MA. Contraception options and provision to adolescents. *Minerva Pediatr.* (2017) 69:403–14. doi: 10.23736/S0026-4946.17.05026-5
70. Wei Y, Liang Y, Lin H, Dai Y, Yao S. Autonomic nervous system and inflammation interaction in endometriosis-associated pain. *J Neuroinflammation.* (2020) 17:80. doi: 10.1186/s12974-020-01752-1
71. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* (2014) 2014:Cd009590. doi: 10.1002/14651858.CD009590.pub2
72. As-Sanie S, Soliman AM, Evans K, Erpelding N, Lanier RK, Katz NP. Short-acting and long-acting opioids utilization among women diagnosed with endometriosis in the United States: a population-based claims study. *J Minim Invasive Gynecol.* (2021) 28:297–306.e2. doi: 10.1016/j.jmig.2020.05.029
73. Estes SJ, Soliman AM, Zivkovic M, Chopra D, Zhu X. The impact of high-risk and chronic opioid use among commercially insured endometriosis patients on health care resource utilization and costs in the United States. *Womens Health.* (2020) 16:1745506520965898. doi: 10.1177/1745506520965898
74. Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* (2017) 10:Cd012509. doi: 10.1002/14651858.CD012509
75. Medicine JH. *Opioid Addiction: What Are Opioids?* Available online at: https://www.hopkinsmedicine.org/opioids/what-are-opioids.html.
76. BPAC. *Understanding the Role of Opioids in Chronic Non-Malignant Pain: bpac nz.* (2017). Available online at: https://bpac.org.nz/2018/opioids-chronic.aspx.
77. Rafique S, Decherney AH. Medical management of endometriosis. *Clin Obstet Gynecol.* (2017) 60:485–96. doi: 10.1097/GRF.0000000000000292
78. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update.* (2009) 15:441–61. doi: 10.1093/humupd/dmp007
79. Koga K, Takamura M, Fujii T, Osuga Y. Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis. *Fertil Steril.* (2015) 104:793–801. doi: 10.1016/j.fertnstert.2015.08.026
80. Long Q, Liu X, Guo SW. Surgery accelerates the development of endometriosis in mice. *Am J Obstet Gynecol.* (2016) 215:320.e1-.e15. doi: 10.1016/j.ajog.2016.02.055
81. Nezhat C, Nezhat F, Nezhat C. Endometriosis: ancient disease, ancient treatments. *Fertil Steril.* (2012) 98:S1–62. doi: 10.1016/j.fertnstert.2012.08.001
82. Brosens I, Benagiano G. Endometriosis, a modern syndrome. *Indian J Med Res.* (2011) 133:581–93. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135985/pdf/IJMR-133-581.pdf
83. Rogers PA, Adamson GD, Al-Jefout M, Becker CM, D'Hooghe TM, Dunselman GA, et al. Research priorities for endometriosis. *Reprod Sci.* (2017) 24:202–26. doi: 10.1177/1933719116654991
84. Kovács Z, Glover L, Reidy F, MacSharry J, Saldova R. Novel diagnostic options for endometriosis - Based on the glycome and microbiome. *J Adv Res.* (2021) 33:167–81. doi: 10.1016/j.jare.2021.01.015
85. Huang L, Liu B, Liu Z, Feng W, Liu M, Wang Y, et al. Gut microbiota exceeds cervical microbiota for early diagnosis of Endometriosis. *Front Cell Infect Microbiol.* (2021) 11:788836. doi: 10.3389/fcimb.2021.788836
86. Wu G, Bersinger NA, Mueller MD, von Wolff M. Intrafollicular inflammatory cytokines but not steroid hormone concentrations are increased in naturally matured follicles of women with proven endometriosis. *J Assist Reprod Genet.* (2017) 34:357–64. doi: 10.1007/s10815-016-0865-3
87. Moses AS, Demessie AA, Taratula O, Korzun T, Slayden OD, Taratula O. Nanomedicines for Endometriosis: lessons learned from cancer research. *Small.* (2021) 17:e2004975. doi: 10.1002/smll.202004975
88. Garzon S, Laganà AS, Barra F, Casarin J, Cromi A, Raffaelli R, et al. Novel drug delivery methods for improving efficacy of endometriosis treatments. *Expert Opin Drug Deliv.* (2021) 18:355–67. doi: 10.1080/17425247.2021.1829589
89. Jiang I, Yong PJ, Allaire C, Bedaiwy MA. Intricate connections between the microbiota and Endometriosis. *Int J Mol Sci.* (2021) 22:5644. doi: 10.3390/ijms22115644
90. Salliss ME, Farland LV, Mahnert ND, Herbst-Kralovetz MM. The role of gut and genital microbiota and the estrobolome in endometriosis, infertility and chronic pelvic pain. *Hum Reprod Update.* (2021) 28:92–131. doi: 10.1093/humupd/dmab035
91. Chadchan SB, Cheng M, Parnell LA, Yin Y, Schriefer A, Mysorekar IU, et al. Antibiotic therapy with metronidazole reduces endometriosis disease progression in mice: a potential role for gut microbiota. *Hum Reprod.* (2019) 34:1106–16. doi: 10.1093/humrep/dez041
92. Chadchan SB, Popli P, Ambati CR, Tycksen E, Han SJ, Bulun SE, et al. Gut microbiota-derived short-chain fatty acids protect against the progression of endometriosis. *Life Sci Alliance.* (2021) 4:e202101224. doi: 10.26508/lsa.202101224

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.