



REVIEW PAPER

## Global risks of endometriosis in women – an appraisal

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### ABSTRACT

**Introduction and aim.** Endometriosis is a complex condition in which endometrium, tissue that resembles the uterine lining, develops outside the uterus. It is considered to be a chronic, estrogen-dependent, inflammatory gynecological disorder having multi-factorial origins. This review paper aims to consolidate recent information on ethnic differences, endometriosis risks, and the disease's etiology in the global context.

**Material and methods.** A systematic search was performed using a variety of international electronic databases, including "PubMed" and "DOAJ", using the terms endometriosis, endometriosis and infertility, endometriosis and cancer, and treatment of endometriosis.

**Analysis of the literature.** Endometriosis can appear anywhere in the body, including the umbilicus, the cecum and ileum of the digestive tract, the breast, the lungs, and the genitourinary organs. It is typically clinically asymptomatic with no obvious clinical manifestation and expensive treatment, which makes the diagnosis late. There is a complex interplay between socio-economic status, family history, societal beliefs and laws, personal habits, reproductive and gynaecological conditions, and environmental influences in the development of endometriosis.

**Conclusion.** Women with endometriosis should be given more attention, and specific resources in the healthcare system should be utilized to provide more efficient multidisciplinary healthcare and treatment.

**Keywords.** endometriosis, hormonal imbalance, infertility

### Introduction

Endometriosis is a complex condition in which endometrium, tissue that resembles the uterine lining, develops outside the uterus, which leads to chronic inflammation, pain, and infertility.<sup>1–9</sup> It affects 190 million women globally who are in reproductive period.<sup>4,8–12</sup> Endometriosis affects around 70 percent of reproductive women who have dysmenorrhea and dyspareunia, and adolescents may have more severe symptoms<sup>13</sup>. However, this figure can be significantly higher because it poses a significant challenge to diagnose the illness correctly.<sup>1,4,7,9,14–17</sup> The schematic presentation of different factors affecting the development of endometriosis is shown in Figure 1. En-

dometriosis is considered to be a chronic, estrogen-dependent, inflammatory gynecological disorders<sup>1,4,7–9,14–18</sup> that may cause severe, life-altering pain during menstruation, inter-menstrual bleeding, painful intercourse, painful bowel movements and urination, as well as persistent pelvic pain, stomach bloating, nausea, exhaustion, depression and anxiety (Fig. 1).<sup>2,4,9,10,13,19–22</sup>

One in nine to ten women experiences endometriosis during their reproductive period.<sup>12,16,21</sup> The symptoms are diverse, but yet many reproductive women are unaware of the disease progression, which makes diagnosis difficulties.<sup>3,9,11,19</sup> Most of the time it is clinically asymptomatic with no obvious clinical manifestation and

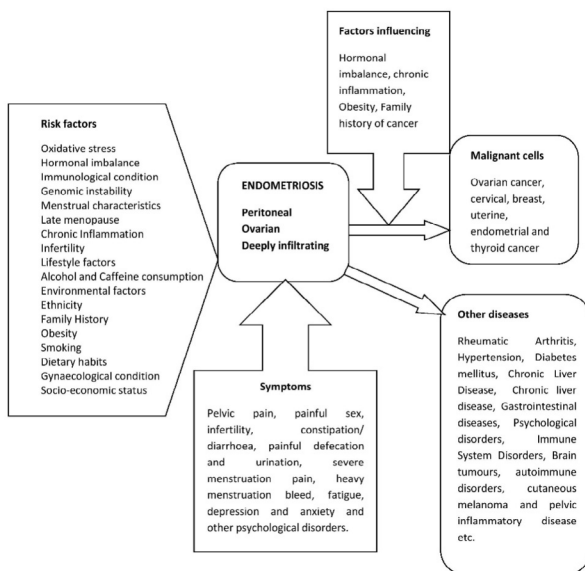
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needs expensive diagnostic tests and treatments.<sup>1,18,19</sup> Endometriosis symptoms are non-specific and can overlap with gastrointestinal and pelvic pain diseases,<sup>2,9,12</sup> and it is associated with a variety of gynecological and non-gynecological co-morbidities such as autoimmune disease, bowel syndrome, migraine, cardiovascular disease, mental disorder, and overall morbidity in reproductive women (Fig. 1).<sup>6,7,9,12,23</sup> Endometriosis is a complex inflammatory condition that affects reproductive women all over the world, from menarche to menopause, regardless of ethnicity or socio-economic status, causing serious reproductive and health consequences.<sup>11,14,24,25</sup> Because endometriosis symptoms typically appear in adolescence, early detection, diagnosis, and treatment of the conditions may reduce pain, halt disease progression, and preserve fertility.<sup>19</sup> Endometriosis can appear anywhere in the body, including the umbilicus, the cecum and ileum of the digestive tract, the breast, the lungs, and genitourinary organs such as the bladder, ureters, vagina, cervix, or the recto-vaginal septum, excluding the spleen.<sup>2,12,15,17,24,26,27</sup> Endometriosis is classified into three types based on where it appears: peritoneal, ovarian, and deeply infiltrating endometriosis.<sup>2,6,7,9,15,18,24,26,27</sup>



**Fig. 1.** Risks factors and association of endometriosis with malignancy and non-communicable diseases

Endometriosis is considered to have multi-factorial origins, which implies that it may have appeared by a combination of factors.<sup>1,9,11,17,22,26,28,29</sup> Several studies have consistently connected a rise in endometriosis incidence to a variety of causes.<sup>19,24</sup> It is hypothesized that endometriosis may arise as a result of the intricate interactions and combined effects of both inherited risks and environmental factors.<sup>8,15,17</sup> Dietary, immunological, and environmental conditions have a significant

impact on the development of endometriosis.<sup>8,15,17,28</sup> Endometriosis risk factors include age, ethnicity, alcohol usage, body mass index, smoking, infertility, hormonal fluctuations, and menstrual characteristics such as early menarche, a shorter and less regular menstrual cycle, dysmenorrhea, menstrual flow intensity, and prolonged estrogen exposure from early menarche to late menopause.<sup>10,16,17,19,21,23,24</sup> Additionally, there is an association between early adult body mass index and endometriosis that is unfavorable.<sup>19,23,27</sup> Several studies have shown possible risk factors such as greater height and low birth weight.<sup>19,27</sup> Notably, although smoking has been proven to either raise or lessen the risk of endometriosis, the association is still not clear.<sup>1,8,19,27</sup>

Dietary factors associated with endometriosis risk may be confounding variables that are amenable to ongoing lifestyle changes. Women are more likely to develop endometriosis than women without first-degree relatives who have the condition to have endometriosis.<sup>27,30</sup> It has been observed that the genetic makeup, hormonal activity, inflammatory state, and immunological environment all have a substantial impact on endometriosis expression and progression.<sup>9,15,19,22,27,28</sup> However, there is a complex interplay between socioeconomic status, family history, societal beliefs, laws, personal habits, reproductive and gynaecological conditions, and environmental influences in the development of endometriosis.<sup>1,8,17,23,27</sup> An increase in pollution and perfluoroalkyl exposure may have an impact on the pathogenesis of endometriosis.<sup>1,27</sup> Experimental investigations revealed that perfluoroalkyl compounds have a detrimental effect on the woman's reproductive system in experimental animals, and are associated with endometriosis.<sup>31</sup> Synthetic fluorinated chemicals are known as Perfluoroalkyl substances and these compounds have been utilized in surfactants, household cleaning goods, textiles, paints, fire-fighting foams, and food packaging because of their hydrophobic and lipophobic qualities.<sup>31</sup> Studies have found that women with higher levels of dioxins and polychlorinated biphenyls in their bodies are more likely to develop endometriosis.<sup>27,31</sup> Despite the fact that these pollutants contribute to the development of the illness, including the production of oxidative stress, further research is required to determine the precise pathways.<sup>1,27</sup>

Exercise and diet are two risk factors for endometriosis that can be addressed.<sup>32,33</sup> Food intervention is one of the most effective self-management strategies for managing endometriosis symptoms, though it is unclear which dietary changes may have an effect on specific types of endometriosis.<sup>29,32</sup> Women suffering from endometriosis may benefit from anti-inflammatory and anti-estrogenic foods by experiencing fewer symptoms.<sup>29,33</sup> Despite the fact that moderate and regular physical activity can help prevent endometriosis, dietary preferences, alcohol and caffeine consumption, smoking, and

intense physical activity have been associated with significantly increased risk factors.<sup>8,16,23,27</sup> Endometriosis risk may be influenced by dietary choices and steroid hormones.<sup>28,32</sup> Fresh fruits and vegetables have been shown to reduce this risk, but other dietary choices, particularly those involving red meat consumption, have been associated with an increased risk of endometriosis.<sup>19,23,24,27,32</sup> However, eating a lot of cruciferous vegetables and taking excess beta-carotene supplements may increase the risk of getting endometriosis.<sup>29</sup> Caffeine and alcohol use can hinder a woman's ability to conceive, which can then affect her reproductive hormones and cause endometriosis to appear.<sup>19,27,29</sup> While severe exercise may promote endometrial proliferation by increasing estrogen levels and insulin-like growth factor-1, moderate exercise may prevent endometrial cancer by lowering inflammation and oxidative stress.<sup>27</sup> In terms of gynaecological and reproductive concerns, the preponderance of endometriosis risk factors are related to parity, menstrual cycle length, flow duration, and age of menarche.<sup>19,24,27</sup> Early menarche and lengthy, intense menstrual cycles are associated with increased risk due to greater levels of estradiol and estrone, whereas parity and oral contraceptive use are associated with protective status.<sup>15,27</sup> Oral contraceptives work by lowering follicular stimulating hormone and stabilizing the endometrium, which relieve endometriosis-related pain by regulating the menstrual cycle and reducing endometrial tissue growth.<sup>12,19,24,34</sup> Thus, women who use oral contraceptives, tubal ligation, and parity are at low risk of developing endometriosis.<sup>12,19,34</sup>

Further, endometriosis alters gene expression in the brain, causing pain sensitization and mood disorders, as well as influencing metabolism in the liver and adipose tissue and promoting systemic inflammation.<sup>35</sup> Furthermore, endometriosis symptoms frequently can also have a negative psychological and social impact on how women act, putting their mental health, sexuality, and interpersonal relationships at risk.<sup>18,24,36</sup> Endometriosis symptoms are exacerbated by psychological factors, and endometriosis women frequently report high levels of anxiety, depression, and other psychological disorders.<sup>3,4,6,7,9,12,36,37</sup> Endometriosis can cause depression and anxiety owing to persistent pain, and the inability to conceive in women.<sup>7,9,12</sup> Their income is negatively impacted by their low productivity, and they exhibit minimal engagement in daily life, relationships, personal affairs, and social activities.<sup>3,6,12,18,24</sup> Endometriosis was identified more than 160 years ago, yet significant scientific gaps remain, including evidence of the disease's etiology.<sup>12</sup> Endometriosis research funding is inadequate, with the National Institutes of Health committing only 0.038% of the health budget for 2022 to a condition that affects nearly 190 million women worldwide, including 6.5 million in the United States.<sup>11,12</sup>

Endometriosis has serious social, public health, and economic consequences. It may reduce women's quality of life owing to extreme pain, exhaustion, melancholy, stress, and infertility.<sup>9,11</sup> Endometriosis discomfort can be so severe that it stops some women from being productive in their daily lives.<sup>12</sup> Hence, it has a significant impact on the woman's mental and socio-emotional health.<sup>9</sup> Endometriosis treatments can minimize absenteeism in the classroom or improve a woman's capacity to work in certain situations.<sup>11</sup> Endometriosis can cause people to stop or avoid sexual activity, impact on their own and their partners' sexual health. Endometriosis treatment and care will empower women by assisting their human right to optimal sexual and reproductive health, quality of life, and overall well-being. Increased awareness, followed by early detection and treatment, may reduce and/or prevent the disease's natural course and lessen the long-term burden of its symptoms, including the risk of increased central nervous system pain sensitivity, but there will be no cure by that time.<sup>9</sup>

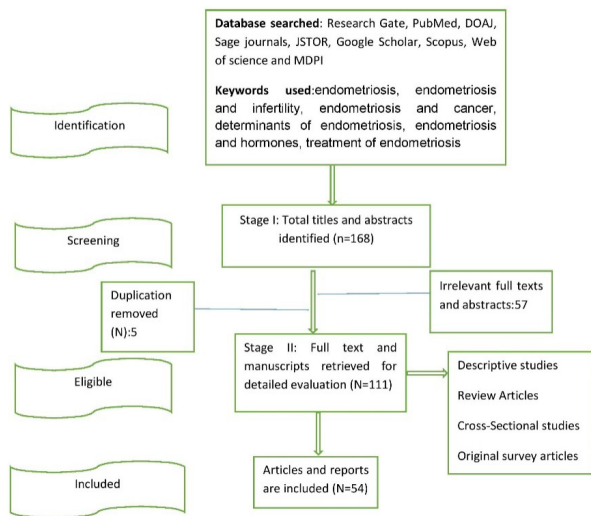
## Aim

Therefore, it is imperative to recognize that this ongoing adverse endometriosis condition is a serious public health concern with severe consequences for women's quality of life and a substantial economic burden. Future research investigation is needed to look into various factors that influence global endometriosis prevalence, which could help with the development of future strategies and intervention programmes. This review manuscript aims to consolidate recent information on ethnic differences, endometriosis risks and the disease's etiology in the global context. In addition, the review manuscript emphasized on how genetic, epigenetic, ethnic differences, environmental and immunological disorders play a part in endometriosis in a broader context.

## Material and methods

A systematic search was performed using a variety of international electronic databases, including "PubMed", "DOAJ", "Google Scholar", "Scopus", "Research Gate", "Web of Science". The primary search terms included endometriosis, endometriosis and infertility, endometriosis and cancer, determinants of endometriosis, endometriosis and hormones, and treatment of endometriosis to find the pertinent literature. All papers relevant to the objective of the present investigation were identified and reviewed after the necessary search. According to a set of criteria, the search papers were evaluated to determine whether they should be included in the current investigation. These criteria included descriptive studies, review articles, cross-sectional studies, original survey studies, etc. This manuscript is a systematic review of the literature published between 2000 and 2022. The search results were limited to full articles

that were published in English. There were no publication date criteria, but new studies were included in this review paper during the manuscript's preparation and final revision. Following the present study keywords criteria and study objectives, a total of 168 publications, including titles, abstracts, and full-texts, were identified. The details of the literature search, inclusion, and exclusion are summarized in Figure 2.



**Fig. 2.** Manuscript identification and selection procedures of the present review study

Manuscripts (N=111) were identified and retrieved for detailed evaluation during the short-listing of published literature and manuscripts. Because a few of the papers were found to be cited in duplicate (N=5), such manuscript duplications were eliminated from the list of publications. Following a thorough review of the published literature, N=54 research papers were identified as appropriate and were considered for the current manuscript. The finalized manuscripts both abstracts and full-length manuscripts, were downloaded in order to interpret the present study, revise, and complete this review manuscript.

## Analysis of the literature

### *Ethnic differences and endometriosis risks*

Endometriosis affects between 10 and 15 percent of women worldwide, according to estimates.<sup>4,8,9,11–13</sup> Endometriosis affected 3,430,094 individuals worldwide in 1990, and 3,785,955 people in 2019, an increase of approximately 10 percent.<sup>38</sup> Endometriosis affects 5–15 percent of women in reproductive age and 2–5 percent of postmenopausal women in Canada and the United States, respectively.<sup>25</sup> It is estimated that more than 4 million women of reproductive age have been diagnosed with endometriosis, according to population-based investigations.<sup>6</sup> Nevertheless, some cases are misdiagnosed, suggesting that endometriosis may affect a greater number of repro-

ductive women.<sup>6</sup> Approximately, 11 percent of American women found to have endometriosis at some point in their lives.<sup>12</sup> In the United States and Australia one out of nine women in their reproductive age has endometriosis.<sup>12</sup> After pelvic inflammatory illness, endometriosis is the third-leading reason for gynecologic hospitalization in the United States.<sup>5,10,32</sup> Endometrial cancer is the most common gynecologic cancer in the United States. According to data, it is also the fourth most common type of cancer among American women.<sup>39</sup> It was predicted that 63,230 women would be diagnosed with this cancer in 2018, with 11,350 dying as a consequence.<sup>39</sup> Endometriosis affects Asian women more than African-American and Caucasian women; medical treatment may make a difference.<sup>5,26,40</sup> Endometriosis was found to be extremely common in developing countries, and it is often underestimated and estimated to affect approximately 42 million women in India.<sup>25</sup> Around 20–25 percent of endometriosis patients are asymptomatic, with only 6–10 percent reporting pelvic pain and 30–50 percent suffering from chronic pain and infertility.<sup>1,4,13,24,38,41</sup> With 10–15 percent of women in reproductive age affected, pelvic endometriosis appears to be one of the most common premenopausal benign gynaecological proliferations.<sup>22,24,42</sup> The symptoms of this chronic gynaecological disorders include persistent pelvic discomfort, unpleasant bowel movements, lower back pain, dyspareunia, infertility, and dysmenorrhea, these symptoms may significantly increase the economic burden and impact socio-economic status and morbidity.<sup>4,7,9,12,13,25,27,41</sup> Endometriosis frequently causes pelvic pain, which has a significant impact on a woman's emotional well-being, general symptoms, and the protracted course of this condition lowers quality of life.<sup>4,12,36,37</sup> Furthermore, there is little evidence that ethnicity influences endometriosis risks.<sup>5,20</sup> It should be noted, however, that these conclusions are based on limited evidence and could be influenced by factors such as healthcare access, diagnostic equipment, and cultural perceptions of women's health issues.<sup>13,38</sup> Ethnicity, along with socio-economic, cultural, and genetic factors, may affect a person's ability to access healthcare and receive proper endometriosis treatment.<sup>5,11</sup>

### *Endometriosis and infertility*

Endometriosis should be taken into account due to its effects on women of reproductive age, has an effect on the reproductive system and decreases their ability to conceive and their fertility.<sup>43</sup> Endometriosis can make pregnancy difficult for women because the growths can interfere with the regular functioning of the ovaries, fallopian tubes, and uterus.<sup>24,43</sup> Endometriosis can cause inflammation, disruption of the normal hormonal balance, and oxidative stress, all of which can interfere with the normal functioning of the reproductive system (e.g., lowering egg quality, interfering with ovulation, and implan-

tation of a fertilized egg) and lead to infertility.<sup>15,24,26,27,43</sup> As a result, even if not related to infertility, treatment and counseling should always be considered and work to preserve patients' chances of pregnancy.<sup>4,43</sup> In terms of female fertility, it has been reported that 30–50 percent of endometriosis patients are infertile due to diminished ovarian reserve, while 25–50 percent of infertile women have endometriosis.<sup>10,12,18,24,26,27,41,43</sup> Endometriosis symptoms and diagnostic probability worsen with age, and incidence is rising among women in the age group of 25–40 years and older.<sup>24,41</sup> The process of oxidative stress contributes significantly by causing chronic inflammation, leading to the deterioration and dysfunction of the reproductive system in endometriosis patients.<sup>43</sup> The connection between infertility and endometriosis is still being researched. Endometriosis-related infertility is now recognized as a multifaceted health problem involving altered immunity and genetics affecting not only the fallopian tubes and embryo transport but also the normal endometrium.<sup>27,43</sup> Medical therapy has been shown to be effective in slowing disease progression.<sup>43</sup> Endometriosis-related infertility is treated with medical and/or surgical intervention, as well as assisted reproduction technology, by reducing or removing the ectopic endometrial implant and restoring normal pelvic anatomy.<sup>27</sup> One of the best remedies for infertility caused by endometriosis has been proven to be in vitro fertilization.<sup>27</sup> Two methods for preserving fertility in women are cryopreservation of embryos and oocytes and cryopreservation of ovarian tissue. At the moment, it appears that oocyte vitrification is the most viable option.<sup>43</sup> Endometriosis treatment may not be beneficial to patients who want to become pregnant. The two suggested treatments in this case are surgery or in vitro fertilization and embryo transfer.<sup>41</sup> Endometriosis patients should have a yearly check-up to determine their ovarian reserve (e.g., anti-mullerian hormone levels, antral follicle count, and cyst size).<sup>43</sup> When endometriosis is first diagnosed, the woman's overall care must be planned, taking the disease's potential impact on her reproductive life into account. Furthermore, modern women are delaying their first pregnancies, which must be considered.<sup>43</sup> The right care must be given, patients must be closely watched, and those who can gain from fertility preservation must be found as soon as possible.<sup>43</sup>

### *Endometriosis and cancer*

Endometriosis may raise a woman's risk of certain cancers, and immune system disorders have also been linked.<sup>9</sup> It raises the risk of ovarian, cervical, breast, uterine, and thyroid cancer (Fig. 1).<sup>2,9,40,44,45</sup> Endometriosis-affected women are more likely to develop ovarian cancer, which is known as endometriosis linked ovarian cancer, especially if they have a prolonged history of the condition and have undergone several op-

erations.<sup>12,17,40,44,45</sup> It is thought that these changes in hormones and inflammation in the body are the causes of the increased risk of ovarian cancer caused by endometriosis, even if the precise mechanisms are still not entirely known. Compared to women without endometriosis, women with endometriosis have a 2–3 percent higher risk of having ovarian cancer.<sup>44–46</sup> Endometriosis-related hormonal imbalances and ongoing inflammation may be to blame for this, which may promote the growth of abnormal cells.<sup>44,45</sup> It's important to remember that the overall risk of ovarian cancer remains low, particularly for women with endometriosis. Furthermore, the relationship between ovarian cancer and endometriosis is still poorly understood. Endometriosis is also associated with an increased risk of endometrial cancer, though this risk is still considered low.<sup>9,45</sup> Ovarian cysts and abnormal cells may be more likely to form in endometriosis-affected women if they also have chronic inflammation, hormone imbalance, obesity, or a family history of endometrial cancer.<sup>4,5,9,47</sup> Endometriosis-associated ovarian cancer development is significant not only because of the danger of infertility, but also because of the possibility of fatal outcomes.<sup>40</sup>

Endometriosis cells eventually transform into malignant cells, and endometriosis risk factors and outcomes, including late menopause and infertility, are observed to be similar for both ovarian cancer and endometriosis.<sup>44</sup> Endometriosis and endometrial cancer are two distinct diseases that affect women and are both regulated by estrogen.<sup>39,46</sup> Endometrial exposure, elevated estrogen production, and low progesterone levels can all cause endometrial hyperplasia, which, if ignored, can turn into endometrial cancer.<sup>39</sup> Endometrial cancer is also more likely to occur in women who have an estrogen-dominant hormonal environment, such as those who are obese, go through menopause later in life, or use estrogen-only hormone replacement therapy. This is because these women's endometrial cells are exposed to high levels of estrogen.<sup>47</sup> Endometriosis is characterized by the formation of tissues that resemble endometrium outside the uterus, whereas endometrial cancer or uterine cancer is made up of carcinoma cells that line the uterus<sup>46</sup>, and pelvic discomfort is the main symptom in both conditions.<sup>46</sup> Additionally, investigations have revealed the association between endometriosis, endometrial cancer, and breast cancer.<sup>45,48</sup> Breast cancer and endometriosis are both chronic, estrogen-dependent gynaecological illnesses that are predisposed by factors related to reproduction and hormone replacement therapy.<sup>46</sup> Endometriosis slightly increases a woman's risk of breast cancer in adulthood, defined as age 50 years or older by twofold compared to a woman without endometriosis.<sup>45,46</sup>

Endometriosis and thyroid issues are pathogenic and can result in hypothyroidism or hyperthyroid-

ism.<sup>7</sup> There is an association between thyroid cancer and endometriosis too, endometriosis patients have a 39 percent increased risk of developing thyroid cancer.<sup>45</sup> Thyroid dysfunction with endometriosis-related infertility was also common in endometriosis.<sup>7,10</sup> Several studies have reported that the uterus has the highest cancer risk, followed by the ovary, cervix, breast, and thyroid. In contrast to other women, endometriosis patients have higher rates of other illnesses including cutaneous melanoma, non-Hodgkin lymphoma, brain tumours, asthma, autoimmune diseases, gastrointestinal disorders such as irritable bowel syndrome, chronic liver disease, diabetes mellitus, hypertension, rheumatoid arthritis, and pelvic inflammatory diseases (Fig. 1).<sup>2,7,9,10,23,26,40</sup>

### *Socio-economic, demographic, and lifestyle determinants of endometriosis*

Regardless of ethnicity and/or socioeconomic status, endometriosis is a complex disorder that affects reproductive women worldwide from menarche to menopause. It is believed that endometriosis has multifactorial causes, which implies that it is brought on by a number of variables.<sup>1,9,11,29</sup> Endometriosis becomes more common with age, and the incidence of endometriosis is inversely related to body mass index.<sup>5,49</sup> Menstrual cycle length, early life factors including preterm delivery, low birth weight and feeding pattern, vitamin D levels, body mass index, specific types of endocrine disruptor chemicals including polychlorinated biphenyls, oral contraceptive pills, mono-2-ethyl-5-hydroxyhexyl phthalate, and ethnicity characteristics are associated with endometriosis.<sup>8</sup> Certain chemicals have been associated with an increased risk of endometriosis in female fetuses during pregnancy; exposure to toxins during pregnancy may also increase their daughters' risk of endometriosis.<sup>1</sup> Endocrine disruptor chemicals, which interfere with the function of the endocrine system, which is a prevalent environmental risk factor found in the environment and food chains.<sup>8</sup> It enters the human body via food, drink, dust, and cosmetics, and its metabolites have been associated with endometriosis and infertility.<sup>1,8,10</sup> Healthy consumption of vitamin D, citrus fruits, dairy products, and long-chain omega-3 fatty acids has been associated with a lower risk of endometriosis.<sup>28,29,33</sup> But, it's unclear whether vitamin D is related to endometriosis symptoms.<sup>29</sup> The risk factors associated with the development of endometriosis are also summarized in Fig. 1. Exercise and omega-3 fatty acids may help prevent endometriosis by lowering inflammatory signs and symptoms, even if there is no direct link between them and the condition.<sup>2,19</sup> Regular exercise is anticipated to lower menstrual flow, stimulate the ovaries, have an estrogen effect, relax the muscles, and lessen pain in endometriosis patients. Moreover, consistent exercise provides an-

ti-inflammatory benefits.<sup>24,33</sup> Endometriosis is positively associated with premenstrual syndrome, dysmenorrhea, and heavy menstrual flow, which are also the symptoms caused by alcoholism.<sup>8</sup>

Dietary factors have been connected to the pathophysiology of endometriosis because of their influence on the steroid hormone metabolism, muscular contraction, inflammatory control, oxidative stress, and menstrual cycle.<sup>28,29</sup> With dietary changes, many women get relief from endometriosis-related symptoms.<sup>29,33</sup> Women with laparoscopically confirmed endometriosis consumed less fresh fruit and green vegetables than women without endometriosis.<sup>1,28</sup> Fresh fruits, particularly citrus fruits, were found to reduce the risk of developing this condition. A diet high in fruits and vegetables is high in provitamin A, which has been linked to lower levels in endometriosis patients.<sup>1,23</sup> The proinflammatory cytokine interleukin-6, which is inhibited by vitamin A, is found in high concentrations in the amniotic fluid of endometriotic women. Citrus fruits are also high in vitamin C, which has anti-inflammatory and antioxidant properties. Fruit consumption has been linked to an increased risk of endometriosis in American women. This could be related to the large amounts of pesticides used during cultivation in the United States.<sup>1</sup> Furthermore, Asian women are more likely than black women to develop endometriosis, and women in industrialized countries with a higher socio-economic level have a higher incidence of this condition.<sup>8,23,24,26</sup> This could be because they have improved healthcare facilities and can thus be diagnosed faster.<sup>8,23,26,38</sup> Endometriosis prevalence and incidence data are scarce or non-existent in many low-income countries and locations.<sup>38</sup>

There was an insignificant association found between eating chicken, fish, shellfish, or eggs and the risk of endometriosis, but the consumption of red meat may increase the risk of endometriosis.<sup>1,19,23,24,28</sup> This effect could be due to the pro-oxidant effects of haemoglobin produced by red meat.<sup>1,19,28</sup> Low levels of sex hormone binding globulin (SHBG) are associated with endometriosis symptoms, while vegetarian women have higher SHBG levels.<sup>1,19,24,28,32</sup> Red meat consumption has been associated with a number of chronic illnesses, such as diabetes, heart disease, and several types of cancer. Red meat consumption has more recently been linked to overall cardio-vascular disease, and cancer mortality.<sup>28,32</sup> The only saturated fatty acid that was positively associated with a higher incidence of endometriosis was palmitic acid.<sup>1,19,32</sup> However, eating a lot of trans-unsaturated fat increased the prevalence of endometriosis, even if eating long-chain omega-3 fatty acids did not.<sup>1,19,28,32</sup> Endogenous estrogen is present in animal fat, which can be decreased by consuming fewer fats.<sup>28,32</sup> Increased estrogen levels are linked to high-fat diets; female bodies create more estrogen in proportion to fat

consumption.<sup>28,33</sup> Eating more red meat is associated with an increased risk of endometriosis,<sup>28,33</sup> independent of heme iron, while heme iron itself is linked to an increased risk of endometriosis.<sup>32</sup> Heme iron is present in myoglobin and hemoglobin derived from animal sources. Non-heme iron is primarily obtained from plants. Although heme iron accounts for a smaller proportion of total iron intake, due to its rapid absorption rate, it can make up to 40 percent of all iron that is absorbed.<sup>32</sup> During retrograde menstruation, erythrocytes are known to discharge haemoglobin and its metabolites, iron and heme, into the peritoneal cavity. If iron and heme are not chelated, they can produce damaging reactive oxygen species, a type of oxidative stress.<sup>28,32</sup> Fish oil has been associated with lower prostaglandin levels, fewer inflammatory symptoms, and a reduction in dysmenorrhea.<sup>28,32</sup> Higher prostaglandin levels are associated with a rise in estrogen production, which may have an impact on how endometrial tissue develops.<sup>28,33</sup> Furthermore, the essential heme iron-carrying protein hemopexin is present at lower levels in the bodies of endometriosis patients.<sup>32</sup> Despite the fact that the physiological mechanism by which nutrition affects endometriosis is not entirely understood, it has been suggested that circulating steroid hormones are involved.<sup>32</sup> Moreover, different foods and nutrients exert different effects on different stages of endometriosis.<sup>29</sup> It is well recognized that endometriosis is brought on by disturbances in the pro-antioxidant balance, which lead to oxidative stress.<sup>1,23</sup>

Due to hormonal changes, pregnancy has a beneficial influence on endometriosis and its related discomfort.<sup>50</sup> Endometriosis is influenced by physiological mechanisms such as breastfeeding; and the length and type of breastfeeding are considered as important factors.<sup>50</sup> Breastfeeding may reduce the risk of endometriosis or be found to have protective effects.<sup>8,50</sup> Benefits of breastfeeding may result from how it influences pituitary hormonal activity, which reduces circulating estrogen levels. In particular, estrogen is crucial for the maintenance and growth of endometriotic lesions.<sup>50</sup> Breastfeeding has been shown to have anti-inflammatory properties that may help in endometriosis prevention and minimize uterine estrogen exposure by slowing ovulation, despite the fact that this topic hasn't received much attention.<sup>8,50</sup> Patients with endometriosis may benefit from prolonged and exclusive breastfeeding, since it can reduce pain feelings and prevent recurrences. The duration and intensity of breastfeeding, in particular, significantly reduces the intensity of any discomfort symptoms.<sup>50</sup> Few studies have examined the impact of breastfeeding on endometriosis, but some have found an opposite association between breastfeeding and the probability of developing endometriosis.<sup>8,50</sup>

### *Hormonal imbalance and endometriosis*

Hormonal fluctuation, especially steroid hormones, has a significant impact on the development and maintenance of endometriosis.<sup>19,26</sup> Younger menstrual women and nulliparous women have higher levels of estradiol and estrone in their blood, which supports the growth of ectopic and eutopic endometrial tissue.<sup>19,51</sup> In both eutopic and ectopic endometrium, estrogen is considered to be the most effective and upstream activator of endometrial tissue survival and inflammation.<sup>15,26,51</sup> Ectopic is the phenotype, and eutopic endometrium is a region of tissue that mimics the uterine lining.<sup>2</sup> Several studies have reported that higher estrogen levels such as estradiol and estrone are associated with an increased risk of endometriosis.<sup>15,43,51</sup> Endometriosis risk in obese women may be explained by the anovulatory cycle, and the retrograde of menstrual blood theories.<sup>19,49</sup> The growth and maintenance of endometriotic tissue, as well as the pain and inflammation brought on by endometriosis, depend on the estrogen 17-estradiol.<sup>15</sup> Patients with endometriosis may have hormonal abnormalities that elevate estrogen levels and raise the possibility of endometrial tissue growth and proliferation, thereby hastening the beginning and development of the condition.<sup>22,43</sup> Patients with endometriosis who have high aromatase activity create more estrogen, which stimulates endometrial tissue growth and multiplication and increases symptoms.<sup>8,15</sup> Aromatase, a cytochrome P450 superfamily enzyme, converts androstenedione and testosterone into estrogens, which is the final step in the formation of the estrogen 17-estradiol.<sup>15</sup> Consumption of alcohol may make the enzyme aromatase more active, which turns testosterone into estrogen, resulting in a drop in testosterone levels and an increase in estrogen levels.<sup>8,23</sup> Additionally, drinking alcohol may prevent the pituitary gland from producing luteinizing hormone, which would increase the ovaries' ability to synthesize estradiol.<sup>8</sup> Aromatase inhibitors significantly lower estrogen levels by preventing the production of estrogen in endometriosis foci and the ovaries.<sup>24</sup> An increase in endogenous estrogen can trigger the development of aromatase P450, which increases endogenous estrogen and prostaglandin levels and exacerbates inflammation in endometriosis.<sup>32</sup> Endometriosis is one of the diseases that can result from hormonal imbalances and significantly affect a woman's reproductive health.<sup>15,19</sup>

Additionally, women with endometriosis may experience pain and discomfort from the hormonal changes brought on by the menstrual cycle.<sup>51</sup> High estrogen levels can hasten the development of endometriosis by causing endometrial tissue to grow and multiply.<sup>51</sup> Luteinizing hormone, androgens, endocrine disruptors and genes influencing sex hormone metabolism are also potential candidate genes for influencing endometriosis onset and progression.<sup>51</sup> Furthermore, high amounts

of androgens may encourage the development of androgen-sensitive endometrial tissue, which would enhance endometriosis growth and proliferation.<sup>27,52</sup> As a result, regulating and treating endometriosis symptoms are dependent on maintaining a balance between these hormones.<sup>15</sup> Hormone therapy allows for both hormone level management and the prevention of endometrial tissue formation, and hormonal contraception and gonadotropin-releasing hormone agonists are two examples.<sup>27</sup> Estrogen is required for the regulation of cyclic gonadotropin release and folliculogenesis.<sup>51,53</sup> Endometriosis is frequently triggered by endocrine disruptor substances, which are abundant in the environment and food chain. However, a few medications interfere with hormonal balance and contribute to the pathophysiology of endometriosis.<sup>1,8</sup>

### *Diagnosis and treatment of endometriosis*

Despite 100 years of research, there is no known cause of endometriosis, nor is there any permanent cure, and treatments mainly focus on managing symptoms.<sup>2,12,18,22,25</sup> Knowing about the inflammatory immune response would aid in a better understanding of this complex condition which could lead to the creation of biomarkers for endometriosis diagnosis because it is implicated in endometriosis pathogenesis.<sup>25</sup> Biomarkers include cell growth, cell survival, high energy requirements, oxidative stress, and fatty acid levels.<sup>16,24</sup> Several biomarkers, including angiogenesis indicators, carcinoma antigen 125 (Ca125), brain derived neurotrophic factor, stem cell markers, steroids, hormones, cytokines, and growth factors, have been examined in relation to endometriosis, but none have shown to be reliable diagnostic tools.<sup>24,27</sup> However, surgical visibility is required for a conclusive and clear diagnosis, although it is difficult to determine the disease's prevalence and incidence.<sup>27</sup> The quality of life of endometriosis patients can be improved by specific combinations of medicinal, surgical, and psychological treatments.<sup>11</sup> To change the hormonal conditions that favour endometriosis, medical treatments concentrate on either reducing estrogen or raising progesterone.<sup>11</sup> Along with medicine, yoga and lifestyle changes significantly affect endometriosis.<sup>21,33</sup> Women with endometriosis who regularly exercise claim it provides them with more energy by increasing the metabolic rate of serotonin neurons in the brain, which may encourage the release of chemicals that improve mood. Exercise is therefore one of the best strategies to raise serotonin levels. Swimming and walking are two exercises that more efficiently raise serotonin levels. These workouts help the body's blood circulation and muscle strength.<sup>24,33</sup>

Endometriosis can recur in postmenopausal women, especially those taking hormone replacement therapy or after a bilateral oophorectomy.<sup>21</sup> There is little evidence that combining medical and surgical treat-

ment improves fertility, and it may cause unnecessary delays in subsequent reproductive care.<sup>22</sup> Modern endometriosis care should be tailored to the individual patient using an interdisciplinary, multimodal, and patient-centered approach.<sup>22</sup> Further, to identify hazards and provide a diagnosis and appropriate treatment, it is essential to comprehend the magnitude of endometriosis in a given community. The requirement for clinical and surgical expertise to appropriately diagnose clinical symptoms, and recognize the presence of ectopic endometrial implants, also known as lesions on the pelvic organs and in the peritoneal cavity, is one of the challenges in reaching a diagnosis.<sup>22</sup> Histological evaluation of lesions removed during laparoscopic surgery continues to be the most accurate way to identify endometriosis, despite the prominence of imaging techniques like transvaginal ultrasonography with intestinal preparation and magnetic resonance imaging.<sup>6,16,21,22,24,43</sup> Due to the vast range of sonographic characteristics, endometriosis lesions may resemble various disorders, such as dermoid cysts, hemorrhagic cysts, neoplasms, ovarian abscesses, and ectopic pregnancies.<sup>27</sup> Consequently, a clear differential diagnosis is necessary to reduce the possibility of misdiagnosis.<sup>27</sup> Endometriosis-related adhesions are most commonly found in the ovaries, uterus, bladder, and fallopian tubes.<sup>2,12,15,17,26</sup> Dysmenorrhea, dyspareunia, pelvic pain, back pain, or weariness are symptoms of early or light stages of the disease, but painful urination, micturition, and blood in the urine are symptoms of more severe stages of impairment.<sup>27,54</sup>

Endometriosis can also manifest clinically as bladder involvement, which can result in cyclic microscopic hematuria in the ureters, recurrent dysuria, and supra-pubic discomfort.<sup>27</sup> Symptoms of gastrointestinal endometriosis can include cycles of abdominal pain, meteorism, tenesmus, constipation, malena, diarrhoea, vomiting, and hematochezia.<sup>27</sup> When endometriosis manifests in unusual anatomical sites like the thoracic cavity, it can result in hemoptysis, pneumothorax, hemothorax, and chest pain.<sup>27</sup> This disease is categorized into three types based on where the endometrial implants are located: peritoneal endometriosis, ovarian endometriosis, and profoundly infiltrative endometriosis.<sup>12,27,43</sup> Endometriosis has the capacity to mimic many other illnesses. Consequently, a complete medical history must be used in conjunction with other specific diagnostic instruments for a correct diagnosis.<sup>27</sup> To diagnose endometriosis, a variety of instruments are required, including surgical methods for direct observation as well as non-invasive imaging methods like ultrasonography and biological cues. Assessing the presence of symptoms and doing a physical examination are the first steps in the diagnosis of endometriosis. Endometriosis cannot be diagnosed with a standard clinical examination alone; further testing, such as laboratory



and imaging procedures, is required to assess the severity and consequences of the disorder.<sup>16,27</sup>

Ultrasound is one of the least expensive, most accessible, and most noninvasive diagnostic methods for identifying endometriosis.<sup>16,27</sup> Transvaginal ultrasonography is the primary imaging modality for detecting ovarian endometriomas due to its high sensitivity and specificity for this purpose.<sup>5,6,27,43</sup> Nonetheless, the gold standard for identifying endometriosis remains laparoscopic examination with histological confirmations.<sup>5,6,12,18,22,27,43</sup> Unfortunately, 10 percent of patients discontinue their medication because of the adverse effects, which include exhaustion, dry vagina, reduced libido, hot flashes, and liver damage.<sup>2,4,17</sup> Along with medication, endometriosis patients also use a wide range of self-management techniques, including self-care, complementary therapies, and dietary adjustments. Relaxation, exercise, meditation, and dietary changes are all part of lifestyle therapy.<sup>29,33</sup> Hence, endometriosis must be managed for the rest of a person's life in order to receive the best medical care and avoid the need for further surgery. The key elements influencing endometriosis treatment technique are the symptoms, age, and fertility of the affected woman.<sup>41</sup> Nowadays, the most prevalent types of treatment are medicinal, surgical, or a combination of these.<sup>41</sup> To improve the current status of endometriosis, a multidisciplinary strategy for early diagnosis, effective treatment, and mental health is required.<sup>26</sup>

## Conclusion

Endometriosis is a multifaceted disorder with numerous forms, sites, and symptoms. Early identification of these conditions have the potential to improve patient response to therapy, reduce complications, and improve women's health by lowering the social, economic, and overall health burden of endometriosis. The period elapsing between being exposed to the substance of interest and developing endometriosis is still unknown and being difficult to pinpoint the exact onset. Endometriosis is poly-etiological, and the reasons are unknown, so it is impossible to rule out the involvement of determinant factors in its pathogenesis. Women with endometriosis should be given more attention, and specific resources or healthcare delivery systems should be utilized to provide efficient multidisciplinary healthcare and treatment. Low-cost, simple early diagnosis screening techniques and effective, non-invasive treatments must be offered in healthcare institutes. It is imperative to limit possible risk factor exposures, identify those who are at risk, and conduct the proper screening by identifying effective disease risk factors, and educating society.

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### Author contributions

Conceptualization, C.R. and N.M; Methodology, C.R.; Software, C.R.; Formal Analysis, C.R. and N.M.; Resources, C.R.; Writing – Original Draft Preparation, C.R.; Writing – Review & Editing, N.M.; Visualization, N.M.; Supervision, N.M.; Funding Acquisition, C.R.

### Conflicts of interest

Authors declare that there are no conflicts of interest.

### Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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